1: Int J Cancer 1994 May 15;57(4):544-52

A cell surface antigen (BAL) defined by a mouse monoclonal antibody inducing apoptosis in a human lymphocytic leukemia cell line.

Wallen-Ohman M, Borrebaeck CA.

Department of Immunotechnology, Lund University, Sweden.

The lack of apoptosis or programmed cell death in human tumor cells has been suggested to be one factor allowing uncontrolled growth of neoplasms. We have developed a mouse monoclonal antibody (MAb) that induces programmed cell death in a human acute leukemia cell line (KM-3) of the pre B-cell type. Stable, antibody-producing hybridomas were produced by fusing mouse myeloma cells to spleen cells from mice immunized with viable KM-3 cells. Incubation of KM-3 cells with the MAb (designated anti-BAL) resulted in growth inhibition and subsequent cell death within 2-3 days. Anti-BAL required cross-linking with a rabbit anti-mouse antibody to induce DNA fragmentation typical of apoptosis. Immunoblotting experiments with anti-BAL identified a 37-kDa protein, apparently different from any previously described apoptosis-related surface antigen. Strongest expression of the antigen was generally found on cells of lymphoid or myeloid origin. However, several other cell types such as fibroblasts and endothelial cells were also stained by anti-BAL in flow cytometry but less intensively. Despite the apparent presence of this cell surface-bound 37-kDa antigen on several normal and malignant cell types, anti-BAL induced cell death only in human malignant cell lines expressing a more immature phenotype.

PMID: 8181858 [PubMed - indexed for MEDLINE]

0020-7136

L12 ANSWER 3 OF 5 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 91065629 MEDLINE
DOCUMENT NUMBER: 91065629 PubMed ID: 2249840
TITLE: **HLA-DR** expression in B-cell **non -Hodgkin**'s malignant lymphomas: a multiparameter flow cytometry study.
AUTHOR: Ratech H
CORPORATE SOURCE: Fox Chase Cancer Center, Department of Pathology, Philadelphia, PA.
CONTRACT NUMBER: CA06927 (NCI)
SOURCE: HUMAN PATHOLOGY, (1990 Dec) 21 (12) 1275-82.
Journal code: 9421547. ISSN: 0046-8177.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19980206
Entered Medline: 19910116

AB Ten cases of reactive follicular hyperplasia and 31 cases of B-cell non-Hodgkin's malignant lymphoma were studied using multiparameter flow cytometry. A bimodal distribution for HLA-DR expression, but not for surface immunoglobulin or B cell-specific antigens CD19 and CD20, was observed commonly in mixed cell type and infrequently in non-mixed cell type B-cell malignant lymphomas. On the basis of HLA-DR distribution alone, 31 cases of B-cell malignant lymphomas of low, intermediate, and high grades could be separated into mixed and non-mixed cell types, with only two misclassifications (P = 0.0001). Exceptionally, one case of malignant lymphoma, follicular and diffuse, mixed-cell type had a unimodal HLA-DR distribution, and one case of malignant lymphoma, diffuse, large noncleaved cell type had a bimodal HLA-DR distribution. In all cases of malignant lymphoma, follicular, mixed-cell type studied, low HLA-DR was correlated with small cells, and high HLA-DR was correlated with large cells. In contrast, HLA-DR expression and cell size were not as directly correlated in cases of malignant lymphoma, diffuse, mixed-cell type. These observations suggest that most, but not all, cases of B-cell malignant lymphomas of the mixed cell type can be separated from other B-cell lymphomas on the basis of HLA-DR distribution.

L12 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 91051817 MEDLINE
DOCUMENT NUMBER: 91051817 PubMed ID: 1700619
TITLE: Cytokine production (IL-1 alpha, IL-1 beta, and TNF alpha) and endothelial cell activation (ELAM-1 and **HLA-DR**) in reactive lymphadenitis, Hodgkin's disease, and in **non-Hodgkin**'s lymphomas. An immunocytochemical study.
AUTHOR: Ruco L P; Pomponi D; Pigott R; Stoppacciaro A; Monardo F; Uccini S; Boraschi D; Tagliabue A; Santoni A; Dejana E; +
CORPORATE SOURCE: Department of Biopathology, University La Sapienza, Rome, Italy.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1990 Nov) 137 (5) 1163-71. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208
Last Updated on STN: 19980206
Entered Medline: 19901211

AB Cryostat sections of 58 lymph nodes were immunostained with a polyclonal rabbit serum against IL-1 alpha, and with monoclonal antibodies directed to IL-1 alpha (Vmp18), IL-1 beta (Vhp20 and BRhC3), and tumor necrosis factor alpha (TNF alpha) (B154.7). Furthermore the presence of cytokine-containing cells was correlated with the expression of endothelial leukocyte adhesion molecule (ELAM-1; 29F2) and of human leukocyte antigen (HLA-DR) (OKIa-1) by endothelial cells. Cells containing IL-1 and/or TNF alpha were detected mainly in pathologic conditions characterized by reactive or neoplastic expansion of the lymph node paracortex. Cells positive for IL-1 were detected in 16 of 21 cases of Hodgkin's disease, in 4 of 4 cases of T-NHL, and in 5 cases of diffuse or mixed lymphadenitis. Interleukin-1 alpha was detected in macrophages, interdigitating reticulum cells (IDRCs), endothelial cells, and neoplastic Hodgkin's and Reed-Sternberg (H-RS) cells. Cells positive for IL-1 beta were much fewer and consisted mainly of macrophages. Hodgkin's Reed-Sternberg cells were negative for IL-1 beta even after in vitro stimulation with bacterial endotoxin. Tumor necrosis factor alpha (TNF alpha) was present in macrophages and H-RS cells. Endothelial leukocyte adhesion molecule-1 expression by endothelial venules was detected in 17 of 20 cases of Hodgkin's disease, in 2 of 4 cases of T-NHL, and in 5 of 5 cases of diffuse lymphadenitis. In these pathologic conditions, HLA-DR antigens also were expressed frequently by endothelial cells. Cytokine-containing cells and ELAM-1-positive high endothelial venules (HEV) were extremely rare in lymph nodes involved by follicular lymphadenitis (12 cases) or B-NHL (16 cases). In cases of reactive or neoplastic B-cell proliferations, HLA-DR-positive HEVs still were present often. Our results indicate that IL-1/TNF alpha production at tissue level is often associated with ELAM-1 expression by HEVs, but is less well correlated with expression of HLA-DR antigens by endothelial cells.

L31 ANSWER 17 OF 24 MEDLINE
ACCESSION NUMBER: 89235235 MEDLINE
DOCUMENT NUMBER: 89235235 PubMed ID: 2523940
TITLE: The targeting of CD4+ T lymphocytes to a B cell lymphoma. A comparison of anti-CD3-**anti-idiotype** antibody conjugates and antigen-**anti-idiotype** antibody conjugates.
AUTHOR: Gravelle M; Ochi A
CORPORATE SOURCE: Division of Molecular Immunology and Neurobiology, Mount Sinai Hospital Research Institute, Toronto, Ontario, Canada.
SOURCE: JOURNAL OF IMMUNOLOGY, **(1989 Jun 1)** 142 (11) 4079-84.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890622

AB We have targeted CD4+ cytotoxic Th (Th/c) lymphocytes to a B cell lymphoma, through the use of a bispecific antibody containing binding sites for both the CD3 complex on the Th/c and the Id on the surface Ig of the B lymphoma (anti-CD3-anti-Id). Cloned, keyhole limpet hemocyanin (KLH)-specific Th/c cells were nonspecifically activated by the anti-CD3-anti-Id conjugate to lyse the Id+ B lymphoma A20-HL. This cytotoxicity was not inhibited by antibodies to CD4 or LFA-1 alpha molecules. The anti-CD3-anti-Id conjugates also induced non-lytic Th clones to become cytotoxic, a function not elicited when these cells were activated specifically by Ag. We compare this model to our previously described system where we targeted the KLH-specific Th/c cells to the Id+ B lymphoma A20-HL via a **conjugate** consisting of **KLH** covalently linked to the anti-Id antibody (KLH-anti-Id). The mechanism involved processing and presentation of KLH by the A20-HL target. This Ag-specific cytotoxicity was MHC class II restricted and was inhibited by antibodies to the CD4 molecule. In both systems, activation of the Th/c cells resulted in bystander killing of tumor but not normal targets. These results may have important implications for the use of Th/c cells in tumor immunotherapy.

L31 ANSWER 20 OF 24 MEDLINE DUPLICATE 10

ACCESSION NUMBER: 92135623 MEDLINE
DOCUMENT NUMBER: 92135623 PubMed ID: 2519837
TITLE: Efficacy of idiotypic vaccination in mice bearing B-cell lymphoma.
AUTHOR: Khan N A
CORPORATE SOURCE: Laboratoire de Cytologie, C.H.U., Faculty of Medicine, Rennes, France.
SOURCE: IN VIVO, **(1989 Mar-Apr)** 3 (2) 117-9.
Journal code: 8806809. ISSN: 0258-851X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920329
Last Updated on STN: 19920329
Entered Medline: 19920309

AB Mice bearing B-cell lymphoma of BCL1 type were vaccinated with idiotype protein (IgM - Id) of IgM lambda type derived from BCL1 malignant cells. Mice were injected with different doses of BCL1 cells (10(3) and 10(6) cells) at the beginning of experimentation. The vaccination was started on days 5, 10 and 15. Mice were injected with either IgM - Id, IgM - Id **conjugated** with **KLH**, IgM - P (IgM lambda obtained from plasmacytoma) or were not immunized. Immunization with IgM - Id **conjugated** with **KLH** was more effective in preventing the death of mice injected with 10(3) and 10(6) cells than IgM - Id or IgM - P alone. There was a higher titre of **anti-idiotype** antibodies in mice immunized with IgM - Id - KLH than in those with IgM - Id only.

L31 ANSWER 22 OF 24 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 87148875 MEDLINE
DOCUMENT NUMBER: 87148875 PubMed ID: 3493524
TITLE: Enhancement and suppression of an intrastrain cross-reactive idiotype.
AUTHOR: Manzo C; Nisonoff A
CONTRACT NUMBER: AI-12895 (NIAID)
AI-17751 (NIAID)
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, **(1987 Feb)** 25 (2) 203-10.
Journal code: 0323767. ISSN: 0300-9475.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198703
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870330

AB The effects of a copolymer of monoclonal **anti-idiotype** (7B7.10) with keyhole limpet haemocyanin (KLH), designated 7-K, on an ongoing immune response were investigated. It was found that the response could be diverted to the production of higher titres of anti-p-azobenzenearsonate (Ar) antibodies, of which nearly 100% carry an intrastrain cross-reactive idiotype (CRIA). The effect was observed only in mice that had received a pre-inoculation of KLH-Ar, or KLH plus bovine gamma globulin-Ar (BGG-Ar). The effect was also observed, however, when cross-linked 7B7.10 was mixed, rather than **conjugated** with **KLH**, suggesting that the role of KLH was to induce the production of a B-cell growth factor. Cross-linked 7B7.10 was not effective in the absence of KLH. A primary inoculation of 7-K together with KLH-Ar did not result in significant suppression or enhancement of CRIA. Also, pre-inoculation of 7-K alone did not suppress a subsequent idiotypic response to KLH-Ar, whereas monomeric anti-Id was suppressive. This supports a possible role for the unmodified Fc segment in the suppressive mechanism. In mice primed with KLH-Ar, before administration of 7-K, CRI+A molecules lacking anti-Ar activity were present in very low concentrations in the immune sera. Larger quantities of such molecules were present in the sera of mice that received 7-K alone. The methods described permit the reproducible production of large amounts of CRI+A anti-Ar antibodies.

L2 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:850772 CAPLUS
DOCUMENT NUMBER: 135:370642
TITLE: Cross-linking of human HLA-DR causes killing of activated B-cells and lymphoid tumor cells
INVENTOR(S): Nagy, Zoltan; Brunner, Christoph; Tesar, Michael; Thomassen-wolf, Elizabeth
PATENT ASSIGNEE(S): Gpc Biotech Ag, Germany; Morphosys Ag
SOURCE: Eur. Pat. Appl., 85 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

1100650

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1156060	A1	20011121	EP 2000-110065	20000512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2001087337	A1	20011122	WO 2001-US15625	20010514
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1289551	A1	20030312	EP 2001-935513	20010514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003032782	A1	20030213	US 2001-1934	20011115

PRIORITY APPLN. INFO.:
EP 2000-110065 A 20000512
US 2000-238492P P 20001006
WO 2001-US15625 W 20010514

AB The authors disclose the prepn. of human Fab fragments which bind to the extracellular domains of the .alpha. and .beta. chains of HLA-DR. Crosslinking of these Fab fragments caused a non-apoptotic killing of B-cell tumor cells and required the cells to be in an activated state. In one example, an IgG construct of the Fab fragments was shown to prolong survival of mice bearing HLA-DR+ tumors.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999294084 MEDLINE
DOCUMENT NUMBER: 99294084 PubMed ID: 10367664
TITLE: Pharmacology and safety assessment of humanized monoclonal antibodies for therapeutic use.
AUTHOR: Klingbeil C; Hsu D H
CORPORATE SOURCE: Preclinical Development Department, Protein Design Labs, Inc., Fremont, California 94555, USA.. cklingbe@pdl.com
SOURCE: TOXICOLOGIC PATHOLOGY, **(1999 Jan-Feb)** 27 (1) 1-3.
Ref: 6
Journal code: 7905907. ISSN: 0192-6233.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

AB The humanization of monoclonal antibodies has generated a class of therapeutic products with improved safety, longer half-lives, and greatly diminished immunogenicity. These engineered proteins are highly species specific and in many cases only cross-react in humans. Where there is cross-reactivity in nonhuman primates or other species, it is not always clear that the pharmacologic effects reflect the potential actions in human volunteers or patients. As with other biologic products, the profile of humanized monoclonal antibodies dictates the preclinical strategy. The preclinical programs for the 2 humanized monoclonal antibodies described here, anti-HLA-DR (**Hu1D10**) and anti-CD3 (HuM291), demonstrate several unique aspects that affected their preclinical development strategy. **Hu1D10** binds to a posttranslational form of HLA-DR and recognizes this antigen in some but not all human and nonhuman primates. The second antibody, HuM291, cross-reacts with CD3 only in the chimpanzee, which is not an optimal test species. In addition, a marketed anti-CD3 product exists (OKT3), and in the preclinical development of our antibody during testing of efficacy and safety, we needed to focus on adverse effects that might be similar to those of OKT3. In these studies, the safety, pharmacokinetics, immunogenicity, and pharmacology (B- and T-cell depletion and recovery) of the 2 antibodies were evaluated. The focus in this review is on the safety and pharmacology testing and the current status of each drug.

L23 ANSWER 4 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2001:74979 SCISEARCH
THE GENUINE ARTICLE: 372WB
TITLE: Enhanced killing of B lymphoma cells by G-CSF-primed effector cells and **Hu1D10** - A humanized antibody against a HLA class II glycosylation variant.
AUTHOR: Stockmeyer B (Reprint); Dechant M; Repp R; Kalden J R; Gramatzki M; Valerius T
CORPORATE SOURCE: Univ Erlangen Nurnberg, Dept Med 3, Erlangen, Germany
COUNTRY OF AUTHOR: Germany
SOURCE: BLOOD, (**16 NOV 2000**) Vol. 96, No. 11, Part 1, pp. 132A-132A. MA 571.
Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA.
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L20 ANSWER 2 OF 31 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:152393 BIOSIS
DOCUMENT NUMBER: PREV200200152393
TITLE: The binding of the humanized antibody Hu1D10 to polymorphic HLA-DR molecules is sequence-dependent.
AUTHOR(S): Chang, Peter W. C. (1); Mugiya, Mond M. (1); Jorgensen, Brett H. (1); Robinson, Thomas J. (1); Motchnik, Paul A. (1); Zhang, Dong (1); Schneider, William P. (1); Tso, J. Y. (1)
CORPORATE SOURCE: (1) Protein Design Labs, Inc., Fremont, CA USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 239b. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The humanized antibody Hu1D10, currently in clinical trials for non-Hodgkin's lymphoma, binds to a polymorphic determinant on the beta chain of the MHC class II molecule HLA-DR. The nature of the 1D10 epitope was determined by (1) amino acid sequencing of the HLA-DR beta chain(s) purified by Hu1D10 affinity chromatography and (2) transfecting individual HLA-DR beta chain genes into mouse DAP.3 cells to assay for Hu1D10 and HLA-DR reactivity. Of the three HLA-DR beta chains expressed in human Raji cells, only the gene product of HLA-DRB*10011 was retained by the Hu1D10 affinity column. This was also the gene that, when expressed in DAP.3 cells, rendered the resulting transfectants Hu1D10-positive. Transfectants expressing the other two **Raji HLA-DR** beta chains are Hu1D10-negative. In addition, two beta chain genes derived from Daudi cells, which are Hu1D10-negative, are Hu1D10-negative when expressed in DAP.3 cells. Transfectants expressing either of two additional genes, HLA-DRB1*0101 and DRB1*04011, are Hu1D10-positive. By recombining Hu1D10-positive and negative genes and expressing the resulting genes in DAP.3 cells, we have determined that the sequence critical to Hu1D10 binding is located within the N-terminal third of the HLA-DR beta chains. We conclude that Hu1D10 specificity is based, at least in part, on polymorphic sequences in HLA-DR beta chains. Residues on HLA-DR critical for Hu1D10 binding are currently being investigated.

L20 ANSWER 8 OF 31 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 94271207 MEDLINE
DOCUMENT NUMBER: 94271207 PubMed ID: 8002991
TITLE: Multiple binding sites on the superantigen, staphylococcal enterotoxin B, imparts versatility in binding to MHC class II molecules.
AUTHOR: Soos J M; Johnson H M
CORPORATE SOURCE: Department of Microbiology, University of Florida, Gainesville 32611.
CONTRACT NUMBER: AI25904 (NIAID)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Jun 15) 201 (2) 596-602.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 19980206
Entered Medline: 19940714

AB To determine MHC class II molecule binding regions of staphylococcal enterotoxin B (SEB), we employed a structurally based approach in which eight overlapping peptides of the entire SEB molecule were synthesized to encompass discrete secondary structures based on the SEB crystalline structure. SEB peptides encompassing amino acid residues 1-33, 31-64 and 179-212 successfully competed with [125I]SEB for binding to DR1 transfected L cells. In contrast, SEB peptides encompassing amino acid residues 1-33, 124-154, 150-183 and 179-212 successfully competed with [125I]SEB for binding to **Raji** cells (**HLA-DR3**, DRw10, DQw1 and DQw2). In addition, the SEB peptide (124-154) inhibited the mitogenic function of SEB. Thus, we have identified multiple regions, including the C-terminus, of SEB that are involved in binding to MHC class II and have shown that these interactions are complex and dependent on the haplotype of the MHC class II molecule.

L23 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:300233 BIOSIS
DOCUMENT NUMBER: PREV200100300233
TITLE: Enhanced killing of B lymphoma cells by G-CSF-primed effector cells and **Hu1D10**: A humanized antibody against a HLA class II glycosylation variant.
AUTHOR(S): Stockmeyer, Bernhard (1); Dechant, Michael (1); Repp, Roland (1); Kalden, Joachim R. (1); Gramatzki, Martin (1); Valerius, Thomas (1)
CORPORATE SOURCE: (1) Dept. Medicine III, University of Erlangen-Nuernberg, Erlangen Germany
SOURCE: Blood, (**November 16, 2000**) Vol. 96, No. 11 Part 1, pp. 132a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Antibody-based immunotherapy appears to become a novel treatment modality for lymphoma patients. Humanized 1D10 (**Hu1D10**) is among the antibodies which are currently evaluated in phase I/II clinical trials in lymphoma patients. 1D10 is directed against a glycosylation variant of HLA class II, which was described to be overexpressed on malignant compared to normal B cells (Gingrich et al. Blood 75:2375, 1990). We found high levels of 1D10 binding on 11/20 (55 %) of leukemic low grade NHL, but also individual patients with 1D10- positive acute leukemias were identified. In addition, normal B cells from 10/15 healthy donors demonstrated low levels of 1D10- reactivity. Previously, we reported that HLA class II antibodies are particularly effective in recruiting polymorphonuclear granulocytes (PMN) as effector cells for killing malignant B cells (Elsaesser et al. Blood 87:3803, 1996). Therefore, we investigated **Hu1D10**- mediated killing of lymphoma cells by granulocyte colony-stimulating factor (G-CSF)- primed effector cells. For this purpose, the 1D10- positive B cell line ARH-77 was used as target in 3 hour 51Cr-release assays. ARH-77 cells expressed similar levels of the CD20 and the 1D10 antigens. With whole blood from healthy donors (HD), increasing concentrations of both **Hu1D10** and rituximab antibodies mediated low levels of target cell killing (see Table 1). Under these assay conditions, both antibodies did not induce complement- mediated lysis. However, **Hu1D10** triggered significantly higher killing by G-CSF-primed blood (G-CSF) compared to rituximab. Analyses of the relevant effector cell populations revealed that FcgammaRI (CD64)- positive PMN were critical for enhanced 1D10- mediated lymphoma killing during G-CSF therapy, while the same effector cell population induced only marginal lysis with rituximab. These preclinical results expand previous studies on the potential of HLA class II as target antigen for lymphoma therapy, and form the basis for a planned phase I/II clinical trial of **Hu1D10** in combination with G-CSF.

L23 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:300235 BIOSIS
DOCUMENT NUMBER: PREV200100300235
TITLE: Rapid redistribution of HLA-DR to membrane rafts induced by humanized mAb 1D10 results in apoptosis of B-cell lymphomas.
AUTHOR(S): Green, Jennifer M. (1); Tso, J. Yun (1)
CORPORATE SOURCE: (1) Protein Design Labs, Inc., Fremont, CA USA
SOURCE: Blood, (**November 16, 2000**) Vol. 96, No. 11 Part 1, pp. 133a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1D10 is a previously described monoclonal antibody that binds to cells from a majority of B-cell malignancies. Studies with transfectants and immunoprecipitation demonstrate that 1D10 recognizes a polymorphic determinant found on the human HLA-DR beta-chain. A humanized version of 1D10 was produced using CDR grafting (**Hu1D10**). Experimental evidence shows that crosslinking HLA-DR with **Hu1D10** induces the direct apoptosis of **Hu1D10**-expressing malignant B cells. In order to understand the mechanism of **Hu1D10**-induced apoptosis of B-cell lymphomas, the intracellular signaling events initiated by **Hu1D10** binding to HLA-DR were investigated. The plasma membrane is known to contain distinct microdomains called membrane rafts, which are highly enriched with glycosphinolipids, cholesterol, and signaling molecules. Rafts may represent a cellular mechanism for the regulation of intracellular signaling via the segregation of membrane constituents and signaling molecules that preferentially associate with these domains. Interestingly, we find that a significant proportion of HLA-DR resides constitutively within membrane rafts and this population is further enriched upon receptor binding with **Hu1D10**. In addition, crosslinking HLA-DR with **Hu1D10** induces the activation of a variety of raft associated signaling molecules including the src-family kinase, lyn, and the non-receptor tyrosine kinase, syk. The syk-inhibitor piceatannol reduces most of the tyrosine phosphorylation events initiated by HLA-DR clustering. Furthermore, **Hu1D10** induced apoptosis is substantially reduced by inhibiting syk activation. Thus, we propose that raft localization and subsequent syk activation are early events in HLA-DR mediated signal transduction leading to programmed cell death.

to sFv-mediated killing. The ability to accomplish selective cytotoxicity of breast cancer cell lines overexpressing the erbB-2 tumor marker should allow for derivation of clinical gene therapy strategies for breast cancer utilizing this approach.

L14 ANSWER 20 OF 25 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 1997-09021 BIOTECHDS
TITLE: New antibodies which induce apoptosis in Her2-expressing cells;
monoclonal antibody production from hybridoma, and humanized antibody engineering for use as an antitumor agent
AUTHOR: Arakawa T; Kita Y A
PATENT ASSIGNEE: Amgen
LOCATION: Thousand Oaks, CA, USA.
PATENT INFO: WO 9720858 **12 Jun 1997**
APPLICATION INFO: WO 1996-US19289 4 Dec 1996
PRIORITY INFO: US 1995-568072 5 Dec 1995
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1997-319726 [29]
AN 1997-09021 BIOTECHDS
AB A new monoclonal antibody, human monoclonal antibody, humanized antibody or F(ab) or Fab' fragment induces apoptosis in cells expressing Her2 (e.g. tumor cells), and recognizes the same epitope on Her2 protein as that recognized by the monoclonal antibody produced by hybridoma ATCC HB 12078. A hybridoma producing the new antibody is also new. The tumor cells are preferably derived from mamma, ovary, prostate, stomach or colorectal cancer. The antibody may be used as an antitumor agent. In an example, BALB/c mice were injected s.c. 3 times at 3-wk intervals with 10 ug soluble Her2, emulsified in RIBI adjuvant. Serum titers against Her2 were evaluated at 8 wk, and the 2 mice with the highest titers were selected and given a final i.v. injection of 10 ug soluble Her2. After 3 days, spleen cells were fused with Sp2/0 mouse myeloma cells, and monoclonal antibody 74 was obtained, which bound to **Her2**. The **antibody** induced **apoptosis** after 24 hr at a concentration of 50 nM in MDAMB453 and MCF7 cells transfected with full-length Her2. (54pp)

L14 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:910136 CAPLUS
DOCUMENT NUMBER: 135:151184
TITLE: Monoclonal antibody therapy for gastric cancer
AUTHOR(S): Sasaki, Shigeru; Imai, Kohzoh
CORPORATE SOURCE: School of Medicine, Sapporo Medical University, Japan
SOURCE: Igaku no Ayumi (**2000**), 195(1), 96-100
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 12 refs. on antitumor activity of chimeric anti-erbB-2 monoclonal antibody CH401 in gastric cancer. Topics included are problems assocd. with monoclonal antibody therapy, Trastuzumab anti-HER2 monoclonal antibody for cancer treatment, erbB-2 gene product as a target mol. for gastric cancer therapy, antitumor activity of chimeric **anti-erbB-2** monoclonal **antibody** CH401, and **apoptosis** induced by **anti-erbB-2** monoclonal **antibody** CH401.

L14 ANSWER 24 OF 25 MEDLINE DUPLICATE 7

ACCESSION NUMBER: 96400216 MEDLINE
DOCUMENT NUMBER: 96400216 PubMed ID: 8806592
TITLE: ErbB receptor activation, cell morphology changes, and **apoptosis** induced by **anti-Her2** monoclonal **antibodies**.
AUTHOR: Kita Y; Tseng J; Horan T; Wen J; Philo J; Chang D; Ratzkin B; Pacifici R; Brankow D; Hu S; Luo Y; Wen D; Arakawa T; Nicolson M
CORPORATE SOURCE: Department of Immunology, Amgen Inc., Amgen Center, Thousand Oaks, California 91320, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1996 Sep 4)** 226 (1) 59-69.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 20000303
Entered Medline: 19961022

AB A panel of mAbs were generated against the purified soluble form of erbB2/Her2 receptor, corresponding to the extracellular region of the receptor, and examined for their ability to mimic the receptor ligand. Some of the mAbs strongly induced tyrosine phosphorylation of 180-185 kDa proteins, including not only Her2 but also Her3 and Her4 receptors, when they were expressed on the surface of breast cancer cells. These mAbs do not cross-react with Her3 or Her4 as demonstrated by competition study. Receptor phosphorylation was also observed with the cell lines transfected with Her2 or a chimeric receptor consisting of the extracellular domain of Her2 and the transmembrane and cytoplasmic domains of epidermal growth factor receptor. Selected mAbs were tested for their ability to change cell morphology, and one specific mAb, mAb74, induced cell morphology changes and apoptosis.

L14 ANSWER 22 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:426995 BIOSIS

DOCUMENT NUMBER: PREV199799726198

TITLE: **Apoptosis** induced by mouse-human chimeric **anti-erbB-2** monoclonal antibody.

AUTHOR(S): Tsujisaki, M. (1); Sasaki, S.; Jinnohara, T.; Ishida, T.; Hinoda, Y.; Imai, K.

CORPORATE SOURCE: (1) First Dep. Internal Med., Sapporo Med. Univ., S1W16 Sapporo Japan

SOURCE: Tumor Biology, (1997) Vol. 18, No. SUPPL. 1, pp. 54.
Meeting Info.: 24th Meeting of the International Society for Oncodevelopmental Biology and Medicine on the Interdependence of Tumor Biology and Clinical Oncology San Diego, California, USA November 17-22, 1996
ISSN: 1010-4283.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L14 ANSWER 21 OF 25 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97319614 MEDLINE
DOCUMENT NUMBER: 97319614 PubMed ID: 9176517
TITLE: An intracellular anti-erbB-2 single-chain antibody is specifically cytotoxic to human breast carcinoma cells overexpressing erbB-2.
AUTHOR: Wright M; Grim J; Deshane J; Kim M; Strong T V; Siegal G P;
Curiel D T
CORPORATE SOURCE: Gene Therapy Program, University of Alabama at Birmingham 35294, USA.
CONTRACT NUMBER: CA 69343-01 (NCI)
SOURCE: GENE THERAPY, **(1997 Apr)** 4 (4) 317-22.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 20000303
Entered Medline: 19970623

AB We previously demonstrated that delivery of a gene encoding an anti-erbB-2 intracellular single-chain antibody (sFv) resulted in down-regulation of cell surface erbB-2 levels and induction of apoptosis in erbB-2 overexpressing ovarian cancer cells. Based upon these findings, we hypothesized that human breast carcinomas overexpressing erbB-2 would be similarly affected by this genetic intervention. We evaluated the phenotypic effects resulting from intracellular expression of the anti-erbB-2 sFv on the human breast cancer cell lines MDA-MB-361, SK-BR-3, BT-474, MCF-7 and MDA-MB-231. Recombinant adenoviruses encoding either a reporter gene (AdCMVLacZ) or the endoplasmic reticulum (ER) directed anti-erbB-2 sFv (Ad21) were delivered to various breast cancer cell lines.

Cell viability was determined by a proliferation assay and fluorescent microscopy allowed visualization of apoptotic cells. An erbB-2 ELISA quantified the endogenous erbB-2 levels of each cell line. The anti-erbB-2 sFv-encoding-adenovirus, Ad21, but not the beta-galactosidase encoding adenovirus, AdCMVLacZ, was cytotoxic to > 95% of the tumor cells in the MDA-MB-361 and SK-BR-3 lines, and > 60% of the tumor cells in the BT-474 line. In marked contrast, the MCF-7 and MDA-MB-231 cell lines showed no change in the rate of cell proliferation following this treatment. The cytotoxic effects generated in the first three lines were a consequence of the induction of **apoptosis** by the **anti-erbB-2** sFv. An ELISA specific for erbB-2 showed that the breast cancer cell lines most susceptible to the anti-erbB-2 sFv, MDA-MB-361, SK-BR-3 and BT-474, overexpressed the erbB-2 protein while the cell lines demonstrating no response to the anti-erbB-2 sFv, MCF-7 and MDA-MB-231, expressed the lowest levels of erbB-2. These results demonstrate that targeted killing of erbB-2 overexpressing cells via intracellular knockout can be accomplished in the context of breast carcinoma. Furthermore, erbB-2 levels in breast tumor cells may be predictive of their sensitivity

ACCESSION NUMBER: 2001087338 PCTFULL ED 20020826
TITLE (ENGLISH): IMMUNOMODULATORY HUMAN MHC CLASS II ANTIGEN-BINDING POLYPEPTIDES

TITLE (FRENCH): POLYPEPTIDES IMMUNOMODULATEURS SE LIANT A L'ANTIGENE HUMAIN MHC DE CLASSE II

INVENTOR(S): **NAGY, Zoltan;**
TESAR, Michael;
THOMASSEN-WOLF, Elisabeth

PATENT ASSIGNEE(S): GPC BIOTECH AG;
MORPHOSYS AG;
NAGY, Zoltan;
TESAR, Michael;
THOMASSEN-WOLF, Elisabeth

DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001087338	A1	20011122

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	**WO 2001-US15626**	**A**	**20010514**
PRIORITY INFO.:	EP 2000-00110063.5		20000512
	US 2000-60/238,762		20001006

L2 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2001087337 PCTFULL ED 20020826
TITLE (ENGLISH): HUMAN POLYPEPTIDES CAUSING OR LEADING TO THE KILLING OF
CELLS INCLUDING LYMPHOID TUMOR CELLS

TITLE (FRENCH): POLYPEPTIDES HUMAINS PROVOQUANT LA MORT DES CELLULES, NOTAMMENT DES CELLULES TUMORALES LYMPHOIDES

INVENTOR(S): **NAGY, Zoltan;**
BRUNNER, Christoph;
TESAR, Michael;
THOMASSEN-WOLF, Elisabeth

PATENT ASSIGNEE(S): GPC BIOTECH AG;
MORPHOSYS AG;
NAGY, Zoltan;
BRUNNER, Christoph;
TESAR, Michael;
THOMASSEN-WOLF, Elisabeth

DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001087337	A1	20011122

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL

	TJ	TM	TR	TT	TZ	UA	UG	US	UZ	VN	YU	ZA	ZW	GH	GM	KE	LS	MW
	MZ	SD	SL	SZ	TZ	UG	ZW	AM	AZ	BY	KG	KZ	MD	RU	TJ	TM	AT	BE
	CH	CY	DE	DK	ES	FI	FR	GB	GR	IE	IT	LU	MC	NL	PT	SE	TR	BF
	BJ	CF	CG	CI	CM	GA	GN	GW	ML	MR	NE	SN	TD	TG				
APPLICATION INFO.:	**WO**	**2001-US15625**						**A**	**20010514**									
PRIORITY INFO.:	EP	2000-00110065.0							20000512									
	US	2000-60/238,492							20001006									

L4 ANSWER 6 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97306279 MEDLINE
DOCUMENT NUMBER: 97306279 PubMed ID: 9162096
TITLE: Diversity associated with the second expressed **HLA**
-DRB locus in the **human**
population.
AUTHOR: Robbins F; Hurley C K; Tang T; Yao H; Lin Y S; Wade J;
Goeken N; Hartzman R J
CORPORATE SOURCE: Naval Medical Research Institute, Bethesda MD 20889, USA.
SOURCE: IMMUNOGENETICS, (1997) 46 (2) 104-10.
Journal code: 0420404. ISSN: 0093-7711.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U31770; GENBANK-U36826; GENBANK-U50061;
GENBANK-U70542; GENBANK-U70543; GENBANK-U70544;
GENBANK-U70545
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19990129
Entered Medline: 19970723

AB Although diversity within the HLA-DRB region is predominantly focused in the DRB1 gene, the second expressed DRB loci, DRB3, DRB4, and DRB5, also exhibit variation. Within DRB1(*)15 or DRB1(*)16 haplotypes, four new variants were identified: 1) two new DRB5 alleles, DRB5*0104 and DRB5*0204, 2) a haplotype carrying a DRB1(*)15 or *16 allele without the usual accompanying DRB5 allele, and 3) a haplotype carrying a DRB5(*)0101 allele without a DRB1(*)15 or *16 allele. The evolutionary origins of these haplotypes were postulated based on their associations with the DRB6 pseudogene. Within HLA haplotypes which carry DRB3, a new DRB3(*)0205 allele and one unusual DRB3 association were identified. Finally, two new null DRB4 alleles are described: DRB4(*)0201N, which exhibits a deletion in the second exon, and a second allele, DRB4(*)null, which lacks the second exon completely. Gene conversion-like events and variation in the number of functional genes through reciprocal recombination and inactivation contribute to the diversity observed in the second expressed HLA-DRB loci.

L4 ANSWER 8 OF 9 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 90293714 MEDLINE
DOCUMENT NUMBER: 90293714 PubMed ID: 1694228
TITLE: Major histocompatibility complex class II-restricted antigen presentation across a species barrier: conservation of restriction determinants in evolution.
AUTHOR: Bontrop R E; Elferink D G; Otting N; Jonker M; de Vries R R
CORPORATE SOURCE: Instituut voor Toegepaste Radiobiologie en Immunologie TNO, Primate Center, Rijswijk, The Netherlands.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1990 Jul 1) 172 (1) 53-9.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19980206
Entered Medline: 19900801

AB The existence of at least three alleles of the **HLA-DRB3** gene within the **human population** is evident. These alleles express DRw52 determinants and react with monoclonal antibody (mAb) 7.3.19.1. The polymorphic epitope recognized by 7.3.19.1 is not only present on human cells but is also expressed on chimpanzee (Pan troglodytes) class II-positive cells. The 7.3.19.1 determinant already existed before speciation of man and chimpanzee, and is at least 5,000,000 yr old. Two-dimensional gel electrophoresis demonstrated that the various HLA- and Patr-DRw52 molecules that are reactive with 7.3.19.1 exhibit isoelectric point differences due to primary amino acid heterogeneity, as was confirmed by sequencing data. Sequence comparison allowed us to map the binding site of mAb 7.3.19.1 to the alpha helix of the major histocompatibility complex (MHC) class II DRB1 domain surrounding the antigen-binding cleft. Despite MHC sequence variation, chimpanzee antigen-presenting cells can present antigen (purified protein derivative) to human T cell lines and vice versa. Only the HLA- and Patr-DRw52 molecules were shown to function as restriction elements for antigen presentation across this species barrier. It is concluded that these particular restriction determinants probably have been conserved in evolution. The HLA- and Patr-DRw52 molecules represent alleles displaying polymorphism that has been selected for in evolution. Such "biomutants" may thus be more useful to study the biological significance of MHC molecules than MHC variants that have been generated by in vitro mutagenesis experiments.

L8 ANSWER 5 OF 127 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000440846 MEDLINE
DOCUMENT NUMBER: 20309222 PubMed ID: 10852382
TITLE: **HLA DRB1***1501 and intrathecal inflammation in **multiple sclerosis**.
AUTHOR: Sellebjerg F; Jensen J; Madsen H O; Svejgaard A
CORPORATE SOURCE: Department of Neurology, University of Copenhagen, Glostrup Hospital, Denmark.. sellebjerg@dadlnet.dk
SOURCE: TISSUE ANTIGENS, **(2000 Apr)** 55 (4) 312-8.
Journal code: 0331072. ISSN: 0001-2815.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000921

L8 ANSWER 6 OF 127 MEDLINE DUPLICATE 4

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:312315 CAPLUS
DOCUMENT NUMBER: 129:66778
TITLE: Association of multiple sclerosis in the Russian population with HLA-DRB1 gene alleles
AUTHOR(S): Sudomoina, M. A.; Boiko, A. N.; Demina, T. L.; Gusev, E. I.; Boldyreva, M. N.; Trofimov, D. Yu.; Alekseev, L. P.; Favorova, O. O.
CORPORATE SOURCE: Russian State Medical University, Russian Federation Ministry of Health, Moscow, 117437, Russia
SOURCE: Molecular Biology (Translation of Molekulyarnaya Biologiya (Moscow)) (1998), 32(2), 255-260
CODEN: MOLBBJ; ISSN: 0026-8933
PUBLISHER: Consultants Bureau
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Multiple sclerosis is a chronic demyelinating disease of the central nervous system presumably of autoimmune nature. Genetic factors play an important role in its etiol. The work describes the results of anal. of the MS genetic susceptibility assocd. with the DRB1 gene region of the major histocompatibility complex (chromosome 6, locus 6p21, HLA class II) carried out by genomic typing for 167 MS patients and 250 healthy controls (all Russians) from the Central region of Russia. A highly reliable assocn. (though weaker than in other Caucasians) was found with the DRB1*1501-*1503 allele group, i.e., with the DR2 (15) specificity, as well as a possible assocn. with the DRB1*0301-*0303 (DR3 specificity) allele group. A marked increase in the relative risk was obsd. for homozygotes DR15/DR15 vs. DR15-contg. heterozygotes, which was indicative of the allele dose effect. Thus, DRB1 and/or some other HLA genes in linkage disequil. with the latter were shown to contribute to the MS susceptibility in the Russian population.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 127 MEDLINE DUPLICATE 10

ACCESSION NUMBER: 2000055429 MEDLINE
DOCUMENT NUMBER: 20055429 PubMed ID: 10610182
TITLE: A humanized model for **multiple sclerosis** using **HLA-DR2** and a human T-cell receptor.
COMMENT: Comment in: Nat Genet. 1999 Nov;23(3):258-9
AUTHOR: Madsen L S; Andersson E C; Jansson L; krogsgaard M; Andersen C B; Engberg J; Strominger J L; Svejgaard A; Hjorth J P; Holmdahl R; Wucherpfennig K W; Fugger L
CORPORATE SOURCE: Department of Clinical Immunology, The Royal Danish School of Pharmacy,Copenhagen, Denmark.
SOURCE: NATURE GENETICS, **(1999 Nov)** 23 (3) 343-7.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20030221
Entered Medline: 19991207

L8 ANSWER 9 OF 127 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 2000117040 MEDLINE
DOCUMENT NUMBER: 20117040 PubMed ID: 10653315
TITLE: Cytokine production in patients carrying **multiple sclerosis**-linked **HLA-DR** alleles.
AUTHOR: Sotgiu S; Serra C; Marrosu M G; Dolei A; Rosati G
SOURCE: JOURNAL OF NEUROLOGY, **(1999 Dec)** 246 (12) 1194-6. Journal code: 0423161. ISSN: 0340-5354.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000209

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L8 ANSWER 21 OF 127 MEDLINE DUPLICATE 12

ACCESSION NUMBER: 1999353195 MEDLINE
DOCUMENT NUMBER: 99353195 PubMed ID: 10426152
TITLE: A study of the **HLA-DR** region in clinical subgroups of **multiple sclerosis** and its influence on prognosis.
AUTHOR: McDonnell G V; Mawhinney H; Graham C A; Hawkins S A; Middleton D
CORPORATE SOURCE: Northern Ireland Regional Neurology Service, Royal Hospitals Trust, Belfast, UK.
SOURCE: JOURNAL OF THE NEUROLOGICAL SCIENCES, **(1999 May 1)** 165 (1) 77-83.
Journal code: 0375403. ISSN: 0022-510X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990920

L8 ANSWER 29 OF 127 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 17

ACCESSION NUMBER: 1999:416921 BIOSIS
DOCUMENT NUMBER: PREV199900416921
TITLE: Preclinical and pharmacological studies of AG284, a soluble **HLA-DR2**:myelin basic protein peptide complex for the treatment of **multiple sclerosis**.
AUTHOR(S): Spack, Edward G. (1); Wehner, Nancy G.; Winkelhake, Jeffrey L.
CORPORATE SOURCE: (1) Megabios Corp., 863A Mitten Rd., Burlingame, CA, 94010 USA
SOURCE: CNS Drug Reviews, (**Fall, 1998**) Vol. 4, No. 3, pp. 225-246.
ISSN: 1080-563X.
DOCUMENT TYPE: General Review
LANGUAGE: English

L8 ANSWER 31 OF 127 MEDLINE DUPLICATE 18

ACCESSION NUMBER: 1998435417 MEDLINE
DOCUMENT NUMBER: 98435417 PubMed ID: 9762669
TITLE: Time-course analysis of CD25 and **HLA-DR** expression on lymphocytes in interferon-beta 1b-treated **multiple sclerosis** patients.
AUTHOR: Ferrarini A M; Sivieri S; Buttarello M; Facchinetti A; Perini P; Gallo P
CORPORATE SOURCE: Department of Neurological and Psychiatrical Sciences, University of Padua, Italy.
SOURCE: MULTIPLE SCLEROSIS, **(1998 Jun)** 4 (3) 174-7.
Journal code: 9509185. ISSN: 1352-4585.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981211

L8 ANSWER 35 OF 127 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 1998261330 MEDLINE
DOCUMENT NUMBER: 98261330 PubMed ID: 9600703
TITLE: Lack of over-expression of T cell receptor Vbeta5.2 in myelin basic protein-specific T cell lines derived from **HLA-DR2** positive **multiple sclerosis** patients and controls.
AUTHOR: Afshar G; Muraro P A; McFarland H F; Martin R
CORPORATE SOURCE: Neuroimmunology Branch, NINDS, National Institutes of Health, Bethesda, MD 20892-1400, USA.
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, **(1998 Apr 1)** 84 (1) 7-13.
Journal code: 8109498. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980601

L8 ANSWER 36 OF 127 MEDLINE

L8 ANSWER 41 OF 127 MEDLINE DUPLICATE 24

ACCESSION NUMBER: 97402872 MEDLINE
DOCUMENT NUMBER: 97402872 PubMed ID: 9258250
TITLE: T cell response to myelin basic protein in the context of the **multiple sclerosis**-associated **HLA-DR15** haplotype: peptide binding, immunodominance and effector functions of T cells.
AUTHOR: Vergelli M; Kalbus M; Rojo S C; Hemmer B; Kalbacher H; Tranquill L; Beck H; McFarland H F; De Mars R; Long E O; Martin R
CORPORATE SOURCE: Neuroimmunology Branch, NINDS, NIH, Bethesda, MD 20892-1400, USA.
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, **(1997 Aug)** 77 (2) 195-203.
Journal code: 8109498. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970826

L8 ANSWER 48 OF 127 MEDLINE DUPLICATE 29

ACCESSION NUMBER: 97057265 MEDLINE
DOCUMENT NUMBER: 97057265 PubMed ID: 8901604
TITLE: Expansion of a recurrent V beta 5.3+ T-cell population in newly diagnosed and untreated **HLA-DR2** **multiple sclerosis** patients.
AUTHOR: Musette P; Bequet D; Delarbre C; Gachelin G; Kourilsky P; Dormont D
CORPORATE SOURCE: Unite de Biologie Moleculaire du Gene, Institut National de la Sante et de la Recherche Medicale U277, Institut Pasteur, Paris, France.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1996 Oct 29)** 93 (22) 12461-6.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
OTHER SOURCE: GENBANK-Y08295
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961224

L8 ANSWER 49 OF 127 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 96:295921 SCISEARCH
THE GENUINE ARTICLE: UA476
TITLE: IMMUNODOMINANT T-CELL RESPONSE TO THE MYELIN BASIC-PROTEIN PEPTIDE-(111-129) IN **HLA-DR4** (B1-ASTERISK-0401)-POSITIVE **MULTIPLE-SCLEROSIS** PATIENTS AND HEALTHY CONTROLS
AUTHOR: MURARO P A (Reprint); VERGELLI M; TRANQUILL L; MARTIN R; MCFARLAND H
SOURCE: NEUROLOGY, (**FEB 1996**) Vol. 46, No. 2, Supp. S, pp. 6025.
ISSN: 0028-3878.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L8 ANSWER 50 OF 127 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 96:400001 SCISEARCH
THE GENUINE ARTICLE: UK861
TITLE: PREVALENCE OF T-CELL REACTIVITY TO MYELIN BASIC-PROTEIN (MBP) PEPTIDE-84-102 IN **HLA-DR2**+ AND **HLA-DR2**- **MULTIPLE-SCLEROSIS** (MS) PATIENTS
AUTHOR: SPACK E (Reprint); MCCUTCHEON M; HSIAO L; TRAN T; WENSKY A; DOAN S; HA T; WEHNER N
CORPORATE SOURCE: ANERGEN INC, REDWOOD CITY, CA, 94063
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (**30 APR 1996**) Vol. 10, No. 6, pp. 2739.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L8 ANSWER 51 OF 127 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 96:399043 SCISEARCH
THE GENUINE ARTICLE: UK861
TITLE: SOLUBLE COMPLEXES OF **HLA-DR2**-MYELIN BASIC-PROTEIN (MBP) PEPTIDE-84-102 INDUCE ANTIGEN-SPECIFIC UN-RESPONSIVENESS IN FRESHLY ISOLATED PERIPHERAL-BLOOD CELLS FROM **MULTIPLE-SCLEROSIS** (MS) PATIENTS
AUTHOR: MCCUTCHEON M (Reprint); WENSKY A; DOAN S; WEHNER N; SPACK E
CORPORATE SOURCE: ANERGEN INC, REDWOOD CITY, CA, 94063
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (**30 APR 1996**) Vol. 10, No. 6, pp. 1782.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L8 ANSWER 54 OF 127 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:348491 BIOSIS
DOCUMENT NUMBER: PREV199699070847
TITLE: Immunodominant T-cell response to the myelin basic protein peptide (111-129) in **HLA-DR4** (B1*0401)-positive **multiple sclerosis** patients and healthy controls.
AUTHOR(S): Muraro, Paolo A.; Vergelli, M.; Tranquill, Laura; Martin, Roland; McFarland, Henry
CORPORATE SOURCE: Bethesda, MD USA
SOURCE: Neurology, (1996) Vol. 46, No. 2 SUPPL., pp. A436-A437.
Meeting Info.: 48th Annual Meeting of the American Academy of Neurology San Francisco, California, USA March 23-30, 1996
ISSN: 0028-3878.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 59 OF 127 MEDLINE DUPLICATE 31

ACCESSION NUMBER: 96074183 MEDLINE
DOCUMENT NUMBER: 96074183 PubMed ID: 7486863
TITLE: Genetic control of **multiple sclerosis**: increased production of lymphotoxin and tumor necrosis factor-alpha by **HLA-DR2**+ T cells.
COMMENT: Comment in: Ann Neurol. 1995 Nov;38(5):702-4
AUTHOR: Zipp F; Weber F; Huber S; Sotgiu S; Czlonkowska A; Holler E; Albert E; Weiss E H; Wekerle H; Hohlfeld R
CORPORATE SOURCE: Department of Neuroimmunology, Max-Planck-Institute, Martinstried, Germany.
SOURCE: ANNALS OF NEUROLOGY, **(1995 Nov)** 38 (5) 723-30.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228

L8 ANSWER 87 OF 127 MEDLINE DUPLICATE 46

ACCESSION NUMBER: 91086843 MEDLINE
DOCUMENT NUMBER: 91086843 PubMed ID: 1702137
TITLE: A myelin basic protein peptide is recognized by cytotoxic T cells in the context of four **HLA-DR** types associated with **multiple sclerosis**
.
AUTHOR: Martin R; Howell M D; Jaraquemada D; Flerlage M; Richert J; Brostoff S; Long E O; McFarlin D E; McFarland H F
CORPORATE SOURCE: Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1991 Jan 1)** 173 (1) 19-24.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19960129
Entered Medline: 19910201

May 14, 2001
May 12, 2000 EP 1156060

US priority

L27 ANSWER 1 OF 18 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-05943 BIOTECHDS
TITLE: Composition for suppressing immune response, treating diseases of immune system, has polypeptide comprising antibody-based antigen-binding domain of human composition, which binds antigen expressed on a cell surface; vector-mediated gene transfer, expression in host cell, antibody library and phage display for recombinant protein production and disease therapy
AUTHOR: NAGY Z; TESAR M; THOMASSEN-WOLF E
PATENT ASSIGNEE: GPC BIOTECH AG; MORPHOSYS AG
PATENT INFO: WO 2001087338 **22 Nov 2001**
APPLICATION INFO: WO 2000-US15626 12 May 2000
PRIORITY INFO: US 2000-238762 6 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-075289 [10]
AN 2002-05943 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A composition (I), comprising a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a cell, where treating cells expressing the antigen with the polypeptides leads to suppression of an immune response, and the IC50 for the suppression of immune response is 1 muM or less, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a pharmaceutical preparation comprising (I) to suppress an immune response in an animal, preferably a human; (2) a nucleic acid (II) including a protein coding sequence for polypeptide of (I); (3) a vector (III) comprising (II) and a transcriptional regulatory sequence operably linked to it; (4) a host cell (IV) harboring (II) or (III); (5) a kit to identify patients treatable with (I), comprising (I) and detector to measure the degree of killing or immunosuppression, IL2 secretion or proliferation of the cells; (6) a diagnostic composition (V) including (I); (7) a kit comprising (I) and a cross-linking moiety, or (V) and a detectable moiety or moieties, reagents and/or solutions to effect and/or detect binding of the moieties to an antigen; (8) a cytotoxic or immunogenic composition comprising (I) operably linked to a cytotoxic or immunogenic agent; (9) conducting a pharmaceutical business, comprising: (a) isolating one or more antibody based antigen-binding domains that bind to major histocompatibility complex (MHC) class II expressed on the surface of human cells with a Kd of 1 muM or less; (b) generating a composition comprising the antibody based antigen-binding domains, which is immunosuppressant with an IC50 of 100 nM or less; (c) conducting therapeutic profiling of the composition for efficacy and toxicity in animals; (d) preparing a package insert describing the use of the composition for immunosuppression therapy; and (e) marketing the composition for use as an immunosuppressant; and (10) conducting a life science business by performing (a) and (b) as above and licensing, jointly developing or selling, to a third party, the rights for selling the composition.

BIOTECHNOLOGY - Preferred Composition: (I) comprises antibody fragments chosen from Fv, scFv, dsFv and Fab fragments, a F(ab')2

antibody fragment or a mini-antibody fragment, or comprises a full antibody chosen from antibodies of classes IgG1, 2a, 2b, 3, 4, IgA and IgM. (I) further comprises a cross-linking moiety or moieties and the antigen-binding sites are cross-linked to a polymer. The polypeptide binds to an epitope in the beta chain of a human leukocyte antigen DR (HLA-DR) molecule, preferably an epitope of the first domain of the beta chain of the HLA-DR. The polypeptide is directed to lymphoid or non-lymphoid cells that expresses MHC class II antigens with Kd of 1 muM or less. Preferred binding domain: The antibody based antigen-binding domain includes a combination of synthetic human combinatorial library (HuCAL) VH2 and HuCAL Vlambda1, where VH CDR3, VL CDR1 and VL CDR3 is found in one of the clones chosen from MS-GPC-1, MS-GPC-2, MS-GPC-3, MS-GPC-4, MS-GPC-5, MS-GPC-6, MS-GPC-7, MS-GPC-8, MS-GPC-10, MS-GPC-11, MS-GPC-14, MS-GPC-15, MS-GPC-16, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41. Preferred Method: The antibody based antigen-binding domain is isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to at least one epitope of human HLA DR, generating a library of variants of at least one of the complementarity determining region 1 (CDR1), CDR2, CDR3 sequences of one or both of the VL and VH domains, and isolation of VL and VH domains from the library of variants by ability to bind to human HLA DR with a Kd of 1 muM or less. The domain binds to at least 3 or 5 different of the HLA-DR types and more preferably to 7 different of the HLA-DR types. The antibody based antigen-binding domain includes a combination of HuCAL VH2 and HuCAL Vlambda1, where the VH CDR3 and VL CDR3 sequence are taken from the consensus CDR3 sequence nnnnRGnFDn and QSYDnnnn, respectively, where n independently represents any amino acid residue, more preferably the VH CDR3 sequence is SPRYGAFDY and/or the VL CDR3 sequence is QSYDLIRH or QSYDMNVH. The VL CDR1 sequence is represented by SGSnnNIGnNYVn, preferably the sequence is SGSESNIGNNYVQ. Preferred Method: (I) has an IC50 for suppressing an immune response, inhibition of IL-2 secretion or T cell proliferation of 1 muM or less. The suppression of an immune response is brought about by or manifests itself in down-regulation of expression of the antigen expressed on the surface of the cell, or in inhibition of the interaction between the cell and other cells, which leads to an immune response. The suppression is brought about by killing of the cells, which is mediated by treating the cells expressing antigen with several antibody based antigen-binding domains which are part of a multivalent polypeptide.

ACTIVITY - Antirheumatic; Antiarthritic; Neuroprotective; Antiinflammatory; Antidiabetic; Antipsoriatic; Immunosuppressive; Dermatological; Antithyroid; Nephrotropic; Thyromimetic; Hepatotropic. **Anti-HLA-DR** antibody fragments selected from the HuCAL library were tested on the HLA-DR positive tumor cell line GRANTA-519. After 4 hours incubation at 37 degrees Centigrade under 6% CO2, cell viability was determined by trypan blue staining and subsequent counting of remaining viable cells. In a control using IgG alone without preincubation with protein G, approximately 55% of cells were killed, while cell killing using IgG pre-incubated with protein G gave a maximum of approximately 75% at a molar ratio of IgG antibody/protein G of approximately 6.

MECHANISM OF ACTION - Suppressor of immune response. No biological

data provided.

USE - (I) is useful for suppressing activation or proliferation of a cell of the immune system, suppressing IL-2 secretion by a cell, the interaction of the cell of the immune system with another cell, immunosuppressing a patient and for killing a cell expressing an antigen, HLA-DR on the surface of the cell, where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to the killing. The killing effects at least 50%, 75% or 85% of activated cells compared to killing of less than 30%, preferably less than 20% or 10% of the non-activated cells. The killing is mediated by an innate pre-programmed process of the cells and is non-**apoptotic**. The killing is independent of caspases that can be inhibited by zVAD-fmk or zDEVD-fmk. (I) (optionally linked to cytotoxic or immunogenic agent) is useful for preparing a pharmaceutical preparation for the treatment of rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's diseases, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulitis, primary biliary cirrhosis, irritable bowel disease and Sjogren's syndrome in humans. By measuring the degree of killing, immunosuppression, IL-2 secretion or proliferation of cells by (I) in a patient, one can identify patients treatable with the composition. (IV) is useful for producing an immunosuppressive composition (all claimed).

ADMINISTRATION - Administration is parenteral, subcutaneous, preferably intravenous, intra-arterial, intramuscular or intraperitoneal.

Dosage not specified.

EXAMPLE - A purified form of a human antigen, the human major histocompatibility complex (MHC) class II DR protein (DRAasterisk0101/DRB1asterisk0401) was prepared from PRIESS cells. Antigen binding antibody fragments of human composition (MS-GPC-1-8, 10, 11, 14, 15 and 16) against the human antigen (DRAasterisk0101/DRB1asterisk0401) were identified from a human antibody library. The synthetic human combinatorial library (HuCAL)-scFv Knappik et al., 2000 library, cloned into a phagemid-based phage display vector pMORPH13(scFv) in Escherichia coli TG-1 was amplified in 2xTY medium containing 34 mug/ml chloramphenicol and 1% glucose. Wells of MaxiSorp microtiter plates were coated with MHC-class II DRAasterisk0101/DRB1asterisk0401 and after blocking with 5% non-fat dried milk in phosphate buffered saline (PBS), 1-5x1012 HuCAL-scFv phage were added for 1 hour at 20 degrees Centigrade. Three rounds of panning and phage amplification were performed. Clones obtained after three rounds of solid phase panning or mixed solid phase/whole cell panning (02.4) were screened by fluorescent activated cell sorting (FACS) analysis on PRIESS cells for binding to human leukocyte antigen DR (HLA-DR) on the cell surface. Only 15 out of over 500 putative binders were identified which specifically bound to PRIESS cells. These clones were further analyzed for immunomodulatory ability and for their killing activity. The sequence characteristics of clones MS-GPC-1-8, 10, 11, 14, 15 and 16 were identified. The Fab-fragment antigen binding polypeptides MS-GPC-1-Fab,

MS-GPC-6-Fab, MS-GPC-8-Fab and MS-GPC-10-Fab were generated from their corresponding scFv fragments. Both heavy and light chain variable domains of scFv fragments were cloned into pMx9Fab and expressed in E.coli cells.

To optimize certain biological characteristics of the HLA-DR binding antibody fragments, one of the Fab fragments, MS-GPC-8-Fab, was used to construct a library of Fab antibody fragments by replacing the parenteral VL lambda1 chain by the pool of all lambda chains lambda 1-3 randomized in CDR3 from the HuCAL library. The resulting Fab optimization library was screened by two rounds of panning against MHC-class II DRAasterisk0101/DRB1asterisk0401. FACS identified optimized clones. Seven of these clones, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18 and MS-GPC-8-27 were further characterized and showed cell killing activity. (139 pages)

L27 ANSWER 2 OF 18 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-06113 BIOTECHDS
TITLE: Polypeptide compositions which bind to cell surface epitopes, which in multivalent form kills lymphoid tumor cells and in monovalent form causes immunosuppression or inhibits activation of lymphocytes;
human major histocompatibility complex class-II antigen-binding HLA-DR protein production by vector-mediated gene transfer and expression in host cell for disease diagnosis and therapy
AUTHOR: NAGY Z; BRUNNER C; TESAR M; THOMASSEN-WOLF E
PATENT ASSIGNEE: GPC BIOTECH AG; MORPHOSYS AG
PATENT INFO: WO 2001087337 **22 Nov 2001**
APPLICATION INFO: WO 2000-US15625 12 May 2000
PRIORITY INFO: US 2000-238492 6 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-075288 [10]
AN 2002-06113 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A composition (I) includes a polypeptide (PP) or a multivalent PP comprising one or more antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on surface of a human cell, especially HLA-DR, where treating cells expressing HLA-DR with multivalent PP causes or leads to killing of cells without need of cytotoxic entities or immunological mechanisms.

DETAILED DESCRIPTION - A composition (I) includes a polypeptide (PP) comprising an antibody-based antigen-binding domain with a binding specificity for human major histocompatibility complex (MHC) class II antigen with Kd of 1 microM or less, where treating cells expressing the antigen with the PP causes or leads to suppression of an immune response.

INDEPENDENT CLAIMS are also included for the following: (1) a pharmaceutical preparation comprising (I) to suppress an immune response, to inhibit interleukin-2 (IL-2) secretion, or T cell proliferation in an animal; (2) a nucleic acid (II) comprising a protein coding sequence for an antigen binding domain comprised in (I) or its multivalent PP; (3) a

vector (III) comprising (II) and a transcriptional regulatory sequence operably linked to it; (4) a host cell (IV) harboring (II) or (III); (5) a kit to identify patients treatable with (I), comprising (I) and a detector to measure the degree of killing or immunosuppression of the cells; (6) a kit comprising (I) and a cross linking group, or (I) and a detectable group, and reagents and/or solutions to effect and/or detect binding of the groups to an antigen; (7) a diagnostic composition including (I) and cross-linking groups; (8) a cytotoxic or immunogenic composition comprising (I) operably linked to a cytotoxic or immunogenic agent; and (9) conducting a pharmaceutical business, by: (a) isolating one or more antibody based antigen-binding domains that bind to antigens expressed on the surface of human cells; (b) generating a multivalent composition such as multivalent PP, comprising several antigen-binding domains, which is immunosuppressant with an IC50 of 100 nM or less and which multivalent composition kills with an EC50 of 50 nM or less transformed or activated cells that express the antigen; (c) conducting therapeutic profiling of the multivalent composition for efficacy and toxicity in animals; (d) preparing a package insert describing the use of the composition for immunosuppression therapy and treatment of proliferative disorders; and (e) marketing the composition for treatment of proliferative disorders and as an immunosuppressant; and (10) conducting a life science business, by performing steps (a) and (b) of the procedure of conducting a pharmaceutical business and licensing, jointly developing or selling, to a third party, the rights for selling the composition.

BIOTECHNOLOGY - Preferred Composition: The multivalent PP has an EC50 for killing transformed or activated cells at least 5-fold lower than the EC50 for killing normal or unactivated cells. The PP has an EC50 of 50 nM or less for killing transformed cells and 10 nM or less for killing lymphoid tumor cells. The EC50 for killing cells of lymphoid tumor cell lines such as KARPAS-422, DOHH-2, SR-7, MHH-CALL-4, MN-60, HD-MY-Z, NALM-1 and LP-1 is 100 nM or less, EC50 for killing cells of the cell line KARPAS-422, DOHH-2, MN-60, NALM-1 and LP-1 is 50 nM or less and EC50 for killing cells from a B cell lymphoblastoid cell line chosen from LG2 and Priess is 10 nM or less. The antigen-binding domain binds to the first domain of the beta-chain of HLA-DR. The antigen-binding domain binds to one or more HLA (human leukocyte antigen)-DR types such as DR1-0101, DR2-15021, DR3-0301, DR4Dw4-0401, DR4Dw10-0402, DR4Dw14-0404, DR6-1302, DR6-1401, DR8-8031, DR9-9012, DRw53-B4asterisk0101 and DRw52-B3asterisk0101. The antigen-binding domain binds to 5 different HLA-DR types. The antibody based antigen-binding domain includes a combination of synthetic human combinatorial library (HuCAL) VH2 and HuCAL Vlambda1, where VH CDR3, VL CDR1 and VL CDR3 is found in one of the clones chosen from MS-GPC-1, MS-GPC-6, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41. The antibody based antigen-binding domain includes a combination of HuCAL VH2 and HuCAL Vlambda1, where the VH CDR3 and VL CDR3 sequence are taken from the consensus CDR3 sequence nnnn Arg Gly n Phe Asp n and Gln Ser Tyr Asp nnnn, respectively, where n independently represents any amino acid residue, more preferably the VH

CDR3 sequence is Ser Pro Arg Tyr Gly Ala Phe Asp Tyr and/or the VL CDR3 sequence is Gln Ser Tyr Asp Leu Ile Arg His or Gln Ser Tyr Asp Met Asn Val His. The VL CDR1 sequence is represented by Ser Gly Ser nn Asn Ile Gly n Asn Tyr Val n, preferably the sequence is Ser Gly Ser Glu Ser Asn Ile Gly Asn Asn Tyr Val Gln. The antibody based antigen-binding domain is isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to at least one epitope of human HLA-DR, generating a library of variants of at least one of the complementarity determining region 1 (CDR1), CDR2, CDR3 sequences of one or both of the VL and VH domains, and isolation of VL and VH domains from the library of variants by ability to bind to human HLA-DR with a Kd of 1 microM or less. The antigen binding domain is a part of a multivalent PP comprising two monovalent antibody fragments chosen from Fv, scFv, dsFv and Fab fragments, a F(ab')2 antibody fragment or a mini-antibody fragment, or comprises a full antibody chosen from antibodies of classes IgG1, 2a, 2b, 3, 4, IgA and IgM. The domain is a part of a multivalent PP that is formed prior to or after binding to a cell. (I) further comprises a cross-linking group and the antigen-binding sites are cross-linked to a polymer. (I) has an IC50 for suppressing an immune response, inhibition of IL-2 secretion or T cell proliferation of 1 microM or less. The suppression of an immune response is brought about by or manifests itself in down-regulation of expression of the antigen expressed on the surface of the cell, or in inhibition of the interaction between the cell and other cells, which leads to an immune response. The suppression is brought about by killing of the cells, which is mediated by treating the cells expressing antigen with several antibody based antigen-binding domains which are part of a multivalent PP.

ACTIVITY - Cytostatic; Antirheumatic; Antiarthritic; Neuroprotective; Antiinflammatory; Antidiabetic; Antipsoriatic; Immunosuppressive; Dermatological; Antithyroid; Nephrotropic; Thyromimetic; Hepatotropic; Muscular-Gen. In vivo therapy was carried out for cancer using an HLA-DR specific antibody. Antigen-binding domains of human composition were used as a therapeutic for the treatment of cancer.

Immunocompromised mice such as scid, nude or Rag-1 knockout were inoculated with DR+ human lymphoma or leukemia cell line of interest. The tumor cell dose 1x10 power 6-1x10 power 7/mouse was established for each tumor tested and administered subcutaneously (s.c.) or intravenously (i.v.). The mice were treated i.v. or s.c. with the IgG form of the **anti-HLA-DR** antibody fragments MS-GPC-8, MS-GPC-8-10-57, MS-GPC-8-27-41 using doses of 1-25 mg/kg over 5 days. Survival of **anti-HLA-DR** treated and control untreated mice was monitored for 8 weeks after cessation of treatment. Tumor progression in the mice inoculated s.c. was additionally quantified by measuring tumor surface area. Significant prolongation of survival of up to 80% of **anti-HLA-DR** treated mice was observed during the experiment, and up to 50% mice survived at the end of

the experiment. In s.c. inoculated and untreated mice, the tumor reached a surface area of 2-3 cm2, while in **anti-HLA-DR** treated animals the tumor surface area was significantly reduced.

MECHANISM OF ACTION - Immune response suppressor; interleukin-2 inhibitor.

USE - (I) (optionally linked to cytotoxic or immunogenic agent), (II) and (IV) are useful for preparing a pharmaceutical preparation for the treatment of cell proliferative disorders, disorders involving transformed cells expressing MHC class II antigens, B cell non-Hodgkin lymphoma, B cell lymphoma, B cell acute lymphoid leukemia, Burkitt lymphoma, Hodgkin lymphoma, hairy cell leukemia, acute myeloid leukemia, T cell lymphoma, T cell non-Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphoid leukemia or multiple myeloid leukemia, disorders involving unwanted activation of the cells of the immune system, such as lymphoid cells expressing MHC class II, rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's diseases, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulitis, primary biliary cirrhosis, irritable bowel disease and Sjogren's syndrome in humans. (I) is useful for suppressing activation or proliferation of a cell of the immune system, suppressing IL-2 secretion by a cell of the immune system, such as expressing HLA-DR, the interaction of the cell of the immune system with another cell, immunosuppressing a patient and for killing a cell expressing an antigen, HLA-DR on the surface of the cell, where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to the killing. The killing is mediated by an innate pre-programmed process of the cells and is non-**apoptotic**. The killing is dependent on the action of non-caspase proteases and/or cannot be inhibited by zVAD-fmk or zDEVD-fmk. By measuring the degree of killing or immunosuppression of cells by (I) in a patient, one can identify patients treatable with the composition. The multivalent PP kills activated lymphoid cells including lymphoid tumor cells representing a disease or from a cell line taken from the list of Priess, GRANTA-519, KARPAS-422, KARPAS-299, DOHH-2, SR-786, MHH-CALL-4, MN-60, BJAB, RAJI, L-428, HDLM-2, HD-MY-Z, KM-H2, L1236, BONNA-12, HC-1, NALM-1, L-363, EOL-1, LP-1, RPMI-8226 and MHH-PREB-1 cell lines, or non-lymphoid cells that express MHC class II molecules. (IV) is useful for producing a composition comprising a multivalent PP that causes or leads to killing of cells (all claimed).

ADMINISTRATION - Administered by parenteral, subcutaneous, preferably intravenous, intraarterial, intramuscular or intraperitoneal route. Dosage not specified.

EXAMPLE - A purified form of a human antigen, the human major histocompatibility complex (MHC) class II DR protein (DRAasterisk0101/DRB1asterisk0401) was prepared from PRIESS cells. Antigen binding antibody fragments of human composition (MS-GPC-1, 6, 8 and 10) against the human antigen (DRAasterisk0101/DRB1asterisk0401) were identified from a human antibody library. The synthetic human combinatorial library (HuCAL)-scFv Knappik et al., 2000 library, cloned

into a phagemid-based phage display vector pMORPH13(scFv) in Escherichia coli TG-1 was amplified in 2xTY medium containing 34 microg/ml chloramphenicol and 1% glucose. Wells of MaxiSorp (RTM) microtiter plates were coated with MHC-class II DRAasterisk0101/DRB1asterisk0401 and after blocking with 5% non-fat dried milk in phosphate buffered saline (PBS), 1-5x10 power 12 HuCAL-scFv phage were added for 1 hour at 20 degrees C. Clones obtained after three rounds of solid phase panning or mixed solid phase/whole cell panning (02.4) were screened by fluorescent activated cell sorting (FACS) analysis on PRIESS cells for binding to HLA-DR on the cell surface. Only 15 out of over 500 putative binders were identified which specifically bound to PRIESS cells. These clones were further analyzed for killing activity. The sequence characteristics of clones MS-GPC-1, 6, 8 and 10 were identified. The Fab-fragment antigen binding polypeptide MS-GPC-1-Fab, MS-GPC-6-Fab, MS-GPC-8-Fab and MS-GPC-10-Fab were generated from their corresponding scFv fragments. Both heavy and light chain variable domains of scFv fragments were cloned into pMx9Fab and expressed in E.coli cells. To optimize certain biological characteristics of the HLA-DR binding antibody fragments, one of the Fab fragments, MS-GPC-8-Fab, was used to construct a library of Fab antibody fragments by replacing the parenteral VL lambda1 chain by the pool of all lambda chains lambda 1-3 randomized in CDR3 from the HuCAL library. The resulting Fab optimization library was screened by two rounds of panning against MHC-class II DRAasterisk0101/DRB1asterisk0401. FACS identified optimized clones. Seven of these clones, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18 and MS-GPC-8-27 were further characterized and showed cell killing activity. (150 pages)

L27 ANSWER 3 OF 18 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2001428347 MEDLINE
DOCUMENT NUMBER: 21369787 PubMed ID: 11477560
TITLE: Humanization and characterization of the **anti-HLA-DR** antibody 1D10.
AUTHOR: Kostelny S A; Link B K; Tso J Y; Vasquez M; Jorgensen B H; Wang H; Hall W C; Weiner G J
CORPORATE SOURCE: Protein Design Labs, Inc., Fremont, CA, USA.
CONTRACT NUMBER: M01 RR00059 (NCRR)
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(2001 Aug 15)** 93 (4) 556-65.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF281860; GENBANK-AF281861
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB 1D10 is a previously described antibody that binds to cells from a majority of B-cell malignancies. The current studies were designed to further evaluate the antigen specificity of 1D10 and its potential as an immunotherapeutic agent. Studies with transfectants and immunoprecipitation demonstrated that 1D10 recognizes some, but not all, of the human HLA-DR beta chains. Both normal and malignant B cells can express the 1D10 antigen. A humanized version of 1D10 was produced using

CDR grafting. The resulting antibody has an affinity that is similar to that of the parental murine antibody. In addition, the humanized antibody is capable of inducing complement-mediated cytotoxicity, antibody-dependent cell cytotoxicity, and direct **apoptosis** of 1D10-expressing B cells. Based on these in vitro anti-tumor activities, we conclude humanized 1D10 deserves further evaluation as an immunotherapeutic agent.

L27 ANSWER 4 OF 18 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:152442 BIOSIS
DOCUMENT NUMBER: PREV200200152442
TITLE: Human HLA-DR monoclonal antibodies that induce **apoptosis** in B cell lymphomas.
AUTHOR(S): Tawara, Tomonori (1); Hirotani, Miki (1); Tahara, Tomoyuki (1); Ishida, Isamu (1); Vidovic, Damir; Laus, Reiner; Kato, Takashi (1); Kataoka, Shiro (1)
CORPORATE SOURCE: (1) Pharmaceutical Research Laboratory, Kirin Brewery Co., Ltd., Takasaki-shi Japan
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 2, pp. 250b. http://www.bloodjournal.org/. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Major histocompatibility complex (MHC) class II-specific antibodies have been reported to induce **apoptosis** of MHC class II-expressing neoplastic cells (Cancer Let 128:127). We have obtained a set of fully human **anti-HLA-DR** monoclonal antibodies (mAbs) from human Ig-transchromosomal mice ("KM mouseTM"), some of which are highly tumorotoxic but not immunosuppressive. These mAbs are of different isotypes (IgG1, IgG2 and IgG3) and they all can induce **apoptosis** of Burkitt's lymphoma Daudi cells in vitro. Since certain MHC class II specific antibodies have been shown to suppress immune responses by inducing **apoptosis** of APCs, downregulating class II expression and/or sterically hindering APC-T cell interactions (J Immunol 164:2379; Eur J Immunol 25:3349), we examined inhibitory effect of our antibodies in mixed leukocyte reaction (MLR) and superantigen-induced proliferation, and found some mAbs not to be inhibitory. Finally, we examined in vivo anti-tumor effects of a selected human mAb. A single 1 mug mAb bolus i.v. dose prolonged the survival of 80% of Raji Burkitt's lymphoma bearing SCID mice for over 10 weeks, while the control Ab-treated mice died within 5 weeks. Thus, our mAb represent hopeful drug candidates for treating HLA-DR-expressing neoplasms.

L27 ANSWER 5 OF 18 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:152414 BIOSIS
DOCUMENT NUMBER: PREV200200152414
TITLE: Prolonged clinical responses in patients with follicular lymphoma treated on a phase I trial of the **anti-**

HLA-DR monoclonal antibody RemitogenTM (Hu1D10.

AUTHOR(S): Link, Brian K. (1); Wang, Hong; Byrd, John C.; Leonard, John P.; Davis, Thomas A.; Flinn, Ian; Hall, William C.; Turner, John F. (1); Bowles, Julie (1); Shannon, Mary (1); Levitt, Daniel; Weiner, George J. (1)

CORPORATE SOURCE: (1) University of Iowa, Iowa City, IA USA

SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 2, pp. 244b. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB The humanized monoclonal antibody Remitogen (Hu1D10), directed against a polymorphic determinant of HLA-DR, is capable of inducing ADCC, complement-mediated lysis, and direct **apoptosis** of lymphoma cell lines and fresh human B-cell tumors (Kostelny et al. Int J Cancer 2001; 93:556-565). In a previous report of a phase I, dose-escalation trial in 20 previously treated B-cell lymphoma patients, we described significant responses in 4 of 8 patients with follicular lymphoma (PR or CRu; Link et al. Proc of Am Soc Clin Oncol 2001; 20:284a). The median time to response was 106 days. This report updates the clinical course and correlative immunologic analysis of responding patients. Methods: In a phase I dose-escalation study, patients with relapsed B-cell lymphoma were treated with 4 weekly infusions of Remitogen at one of 4 dose levels (3-6 patients each): 0.15 (level 1); 0.5 (level 2); 1.5 (level 3); and 5 mg/kg (level 4). A daily crescendo regimen was also tested (1.5, 3.5, 5, 5, 5 mg/kg/day over 5 days (level 4a)). Patients were initially monitored for toxicity, pharmacokinetics, and tumor response through day 100. Subsequent clinical evaluations were at the discretion of the investigators. Results: No late toxicities or unexpected infections have been observed. Four partial responses have been documented among 8 patients with follicular lymphoma treated on the weekly schedule (2/4 patients at dose level 2), (1/4 patients at dose level 3) and (1/3 patients at dose level 4). Three of these patients had previously been refractory to therapy with rituximab. Two patients achieved radiographic criteria for CRu, although subsequent bone marrow evaluations documented residual disease. One of the responding patients relapsed at 21 months from initiation of therapy. His disease remained refractory to multi-agent chemotherapy and he is being re-treated with Remitogen on a compassionate basis. Three other responders remain progression-free at 13, 17 and 21 months. Single cell suspensions of lymphoma cells harvested prior to therapy were available from two responding patients. These cells were used to assay for the presence of autologous anti-lymphoma IgG. There was no autologous anti-lymphoma IgG in serum obtained prior to Remitogen therapy or 50 days after therapy. In contrast, day 100 serum from one of these patients contained autologous anti-lymphoma IgG, suggesting this patient had developed an active humoral anti-lymphoma immune response. We conclude Remitogen can induce durable

remissions in patients with follicular lymphoma and that a unique mechanism of action may be contributing to this response. A Phase II study is ongoing at dose levels 2 and 3, as are correlative assays exploring mechanisms of action of Remitogen.

L27 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:161333 CAPLUS
DOCUMENT NUMBER: 132:206948
TITLE: Selective **apoptosis** of neoplastic cells by an HLA-DR specific monoclonal antibody
INVENTOR(S): Vidovic, Damir; Laus, Reiner
PATENT ASSIGNEE(S): Dendreon Corporation, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012560	A1	20000309	WO 1999-US19628	19990826 <--
AU 9955880	A1	20000321	AU 1999-55880	19990826 <--
US 2001053360	A1	20011220	US 2001-929209	20010813 <--
US 6416958	B2	20020709		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1998-98292P P 19980828
US 1999-383663 A3 19990826
WO 1999-US19628 W 19990826

AB The authors disclose the prepn. and biol. activity of **anti-HLA-DR**-specific monoclonal antibodies which induce **apoptosis** of HLA-DR pos. tumor cells. The antibodies bind to the first extracellular domain and eliminate tumor cells by crosslinking surface HLA-DR. In one example, the monoclonal antibody Danton (IgG1) was shown to prolong the survival of SCID mice inoculated with a plasmacytoma cell line.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001069319 MEDLINE
DOCUMENT NUMBER: 20519587 PubMed ID: 10948188
TITLE: Ligation of HLA-DR molecules on B cells induces enhanced expression of IgM heavy chain genes in association with Syk activation.
AUTHOR: Tabata H; Matsuoka T; Endo F; Nishimura Y; Matsushita S

CORPORATE SOURCE: Division of Immunogenetics, Department of Neuroscience and Immunology, Kumamoto University Graduate School of Medical Sciences and the Department of Pediatrics, Kumamoto University School of Medicine, Kumamoto 860-0811, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(2000 Nov 10)** 275 (45) 34998-5005.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010104

AB Signals transmitted by class II major histocompatibility complex are important regarding cell function related to antigen presentation. We examined effects of DR-mediated signaling on Ig production from B cells. Cross-linking HLA-DR molecules on B cells by solid-phase **anti-HLA-DR** monoclonal antibodies, led to an increased production of IgM, without proliferation or **apoptosis**. This event was accompanied by an enhanced expression of both membrane- and secretory-type IgM heavy chain mRNA. When peptide-pulsed B cells were co-incubated with an HLA-DR-restricted T cell clone treated by the protein synthesis inhibitor emetine, peptide-induced de novo expression of lymphokines and cell-surface molecules on T cells can be neglected. CD40-CD154 interaction was not involved in IgM enhancement, in such a system. The protein-tyrosine kinase inhibitors and the Syk inhibitor piceatannol, but not the Src inhibitor PP2 had a marked inhibitory effect on IgM secretion. Furthermore, ligation of HLA-DR on B cells using the F(ab')2 fragment of **anti-DR** monoclonal antibody, enhanced Syk activity. Our data suggest that HLA-DR on B cells not only present antigenic peptides to T cells, but also up-regulate IgM production, in association with Syk activation and without the involvement of Src kinases, hence the possible physiological relevance of Src-independent Syk activation.

L27 ANSWER 8 OF 18 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000241576 MEDLINE
DOCUMENT NUMBER: 20241576 PubMed ID: 10780664
TITLE: CD4+ T cell-mediated cytotoxicity toward thyrocytes: the importance of Fas/Fas ligand interaction inducing **apoptosis** of thyrocytes and the inhibitory effect of thyroid-stimulating hormone.
AUTHOR: Kawakami A; Matsuoka N; Tsuboi M; Koji T; Urayama S; Sera N; Hida A; Usa T; Kimura H; Yokoyama N; Nakashima T; Ishikawa N; Ito K; Kawabe Y; Eguchi K
CORPORATE SOURCE: The First Department of Internal Medicine, Nagasaki University School of Medicine, Tokyo, Japan.
SOURCE: LABORATORY INVESTIGATION, **(2000 Apr)** 80 (4) 471-84.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000509

AB The accumulation of activated CD4+ T cells and antigen (Ag)-dependent cellular interactions between thyrocytes and CD4+ T cells have been determined in thyroid gland from patients with Graves' disease. The Fas/Fas ligand (FasL) interaction between antigen-presenting cells and T cells regulates the **apoptosis** of the former cells triggered by the latter cells. The inhibition of Fas-mediated **apoptosis** in thyrocytes could be a underlying mechanism of hyperplasia of thyrocytes in patients with Graves' disease. We investigated the potential role of Fas/FasL interaction between thyrocytes and CD4+ T cells in the induction of Fas-mediated **apoptosis** of the former cells induced by the latter cells. The presence of only a few specific T cells responsive to a putative autoantigen has hampered the investigation of specific T cell activation toward antigen-presenting cells (APCs). Therefore, we used a superantigen, staphylococcal enterotoxin B (SEB), to examine specific T cell activation toward thyrocytes in vitro since it stimulates a large proportion of T cells with particular Vbeta elements. Spontaneous **apoptosis** of thyrocytes in culture was not found even in the presence of various kinds of cytokines. In contrast, a clear induction of Fas-mediated **apoptosis** by anti-Fas IgM was determined in interferon-gamma (IFN-gamma)-stimulated thyrocytes. In addition, a significant cytotoxicity of purified CD4+ T cells toward IFN-gamma-stimulated thyrocytes in the presence of SEB was induced, and the addition of **anti-HLA-DR** and -DQ monoclonal antibodies (mAbs) or blockade of the Fas/FasL interaction reduced this cytotoxicity. FasL expression of CD4+ T cells cocultured with IFN-gamma-stimulated thyrocytes in the presence of SEB was clearly induced. Furthermore, the addition of mAbs against CD54 and CD58 inhibited both cytotoxicity and FasL expression of CD4+ T cells. The cytotoxicity of CD4+ T cells toward IFN-gamma-stimulated, SEB-pulsed thyrocytes was markedly inhibited when we used thyrocytes cultured with IFN-gamma in the presence of thyroid-stimulating hormone (TSH) as target cells. Our results suggest that 1) CD4+ T cells were activated by thyrocytes expressing MHC class II molecules in an SEB-dependent manner and then expressed FasL. 2) These activated FasL+ CD4+ T cells killed thyrocytes by interacting with Fas on thyrocytes and FasL on activated CD4+ T cells. The presence of costimulating molecules such as CD54 and CD58 on thyrocytes was also necessary to generate activated FasL+ CD4+ T cells. 3) Since the actions of thyroid stimulating antibody (TSAb) toward thyrocytes are similar to those of TSH, one goitrogenic activity of TSAb may, in part, be due to the inhibitory effect on Fas-mediated **apoptosis** of thyrocytes triggered by activated CD4+ T cells.

L27 ANSWER 9 OF 18 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:199431 BIOSIS
DOCUMENT NUMBER: PREV200100199431
TITLE: CD4+ T cell-mediated cytotoxicity toward thyrocytes: The importance of Fas/Fas ligand interaction inducing **apoptosis** of thyrocytes and the inhibitory effect

of TSH.

AUTHOR(S): Kawakami, A. (1); Hida, A. (1); Yamasaki, S. (1); Nakashima, T.; Sera, N. (1); Usa, T. (1); Ida, H. (1); Ashizawa, K. (1); Ejima, E. (1); Migita, K. (1); Ishikawa, N.; Ito, K.; Eguchi, K. (1)

CORPORATE SOURCE: (1) First Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, 852-8501 Japan

SOURCE: Endocrine Journal, (**August, 2000**) Vol. 47, No. Suppl. August, pp. 122. print.
Meeting Info.: 12th International Thyroid Congress Kyoto,, Japan October 22-27, 2000 British Society of Gastroenterology
. ISSN: 0918-8959.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L27 ANSWER 10 OF 18 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2000017808 MEDLINE

DOCUMENT NUMBER: 20017808 PubMed ID: 10551646

TITLE: Recognition of major histocompatibility complex class II antigens by two **anti-HLA-DR** monoclonal antibodies on canine marrow cells correlates with effects on in vitro and in vivo hematopoiesis.

AUTHOR: Yamaguchi M; McSweeney P A; Kimball L; Gersuk G; Hong D S; Kwok W; Storb R; Beckham C; Deeg H J

CORPORATE SOURCE: Clinical Research Division, Fred Hutchinson Cancer Research
Center, Seattle, Washington 98109, USA.

CONTRACT NUMBER: CA18029 (NCI)
CA18221 (NCI)
CA31787 (NCI)
+

SOURCE: TRANSPLANTATION, **(1999 Oct 27)** 68 (8) 1161-71.
Journal code: 0132144. ISSN: 0041-1337.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199911

ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991116

AB BACKGROUND: The role of major histocompatibility complex class II antigens in hematopoiesis is not well defined. We have shown that in vitro depletion of HLA-DR+ cells from canine marrow (e.g., by **anti-HLA-DR** monoclonal antibody [mAb] H81.9 and complement) prevents hematopoietic recovery. In vivo administration of the same mAb H81.9 after transplantation of unmanipulated autologous marrow results in graft failure. In vitro mAb H81.9 inhibited colony formation from short-term and long-term marrow cultures. METHODS AND RESULTS: We investigated the effect of another mAb, Ca1.41, which also recognizes nonpolymorphic determinants on human (HLA-DR) and canine major histocompatibility complex class II antigens but is reactive with a narrower spectrum of cells in both canine peripheral blood and marrow than

mAb H81.9 (and other **anti-HLA-DR** mAbs). In contrast to all other **anti-HLA-DR** mAbs tested, Ca1.41 did not interfere with colony formation in short-term or long-term marrow cultures and spared a population of small mononuclear cells with low forward light scatter that was eliminated via **apoptosis** by exposure to mAb H81.9. These target cells included lymphocytes and CD34+ hemopoietic precursors that expressed MHC class II molecules as determined by mAb H81.9 but not by mAb Ca1.41. In addition, transmembrane signaling and up-regulation of interleukin-1beta mRNA occurred with mAb H81.9 but not with Ca1.41. Transplantation of autologous marrow treated in vitro cytolytically with mAb Ca1.41 allowed for complete hematopoietic reconstitution. Further, in vivo administration of Ca1.41 posttransplant did not lead to autologous graft failure as had been observed with mAb H81.9. CONCLUSIONS: These results support the notion that major histocompatibility complex class II is expressed on early hematopoietic precursor cells but recognition is dependent upon the mAb used. Preliminary studies show that mAb H81.9 triggered transmembrane signaling, resulting in up-regulation of interleukin-1beta and **apoptosis**, although mAb Ca1.41 did not. The fact that Ca1.41 binding was modified in the presence of exogenous invariant chain-derived peptide suggests that both binding and signaling are peptide dependent.

L27 ANSWER 11 OF 18 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000030870 MEDLINE
DOCUMENT NUMBER: 20030870 PubMed ID: 10566594
TITLE: HLA-DR inhibits granulocytic differentiation without inducing **apoptosis** of CD34 cells.
AUTHOR: Bertho N; Drenou B; Mooney N; Amiot L; Langanay T; Le Berre C; Charron D; Fauchet R
CORPORATE SOURCE: Laboratoire Universitaire d'Hematologie et de Biologie des Cellules Sanguines, INSERM CRI 4U006B-UPRES EA 22-33, Rennes, France.
SOURCE: HUMAN IMMUNOLOGY, **(1999 Oct)** 60 (10) 944-54.
Journal code: 8010936. ISSN: 0198-8859.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991206

AB Hematopoietic progenitors express HLA-DR molecules. However the significance of HLA-class II molecules on CD34+ cells remains unknown. The primary role of HLA-class-II molecules is antigen presentation although a second role, that of signal transduction, has been established in B cells. The role of HLA-DR in hematopoiesis was examined by determining the ability of CD34+ progenitor cells to differentiate to "Colony Forming Unit Granulocyte-Macrophage" (CFU-GM) and "Burst Forming Unit Erythrocyte" (BFU-E) in the presence of **anti-HLA-DR** monoclonal antibody. We observed a reduction in the number of CFU-GM which

was due in part to down regulation of granulocyte rather than monocyte differentiation. These observations suggest that HLA-DR signals can regulate myelopoiesis. We point out especially the role of the HLA-DR molecule in the switch of CFU-GM between granulocyte or monocyte lineages.

Although HLA-DR mediated **apoptosis** has been described in mature B lymphocytes **apoptosis** of CD34+ cells was excluded as a mechanism.

L27 ANSWER 12 OF 18 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000073978 MEDLINE
DOCUMENT NUMBER: 20073978 PubMed ID: 10608299
TITLE: Induction of negative regulators of haematopoiesis in human bone marrow cells by HLA-DR cross-linking.
AUTHOR: Yamaguchi M; Nadler S; Lee J W; Deeg H J
CORPORATE SOURCE: Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
CONTRACT NUMBER: CA09515 (NCI)
CA18029 (NCI)
HL36444 (NHLBI)
SOURCE: TRANSPLANT IMMUNOLOGY, **(1999 Sep)** 7 (3) 159-68.
Journal code: 9309923. ISSN: 0966-3274.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000207

AB Tumour necrosis factor-alpha (TNF alpha) is up-regulated by cross-linking of major histocompatibility complex (MHC) class II [human leucocyte antigen (HLA)-DR] antigens on monocytes. This is done by a bacterial superantigen or **anti-HLA-DR** monoclonal antibody (MAb). We have previously shown that HLA-DR cross-linking results in inhibition of haematopoiesis and **apoptosis**. TNF alpha acts as a negative regulator of haematopoiesis. Here we investigated whether HLA-DR-mediated inhibition of haematopoiesis involved TNF alpha and TNF alpha-dependent secondary signals. **Anti-HLA-DR** MAb H81.9 up-regulated TNF alpha, as well as transforming growth factor beta, interleukin (IL)-1beta and IL-6 in human marrow cells at the ribonucleic acid (RNA) and protein level. The effect on TNF alpha was investigated further. Up-regulation was blocked by herbimycin A, consistent with a tyrosine kinase-dependent mechanism. Up-regulation was also blunted by the soluble TNF-receptor fusion protein TNFR:Fc, suggesting an autocrine amplification loop. Following TNF alpha up-regulation, there was increased expression of Fas (CD95) and Fas-ligand (Fas-L). Up-regulation of Fas and Fas-L was blocked by TNFR:Fc. Furthermore, MAb H81.9-induced **apoptosis** was prevented by anti-TNF alpha MAb and by the soluble Fas receptor, Fas-Ig, providing further evidence that the TNF effect was mediated via Fas. At the transcriptional level, cross-linking of HLA-DR by MAb H81.9 affects nuclear localization of NFkappaB, which is involved in the transcription of TNF alpha. NFkappaB activity is modified by changes in cellular redox

potential, and we have shown that H81.9 affects redox potential as determined by the generation of nitric oxide. These data show that HLA-DR-initiated signals are able to trigger a cascade of negative regulators of haematopoiesis. This model provides an opportunity to dissect signalling pathways that may be involved in the development of spontaneous marrow failure, and to devise interventions aimed at protecting haematopoiesis.

L27 ANSWER 13 OF 18 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999069251 MEDLINE
DOCUMENT NUMBER: 99069251 PubMed ID: 9767455
TITLE: CD4+ T-cell-mediated cytotoxicity against staphylococcal enterotoxin B-pulsed synovial cells.
AUTHOR: Kawakami A; Matsuoka N; Tsuboi M; Urayama S; Nakashima T; Kawabe Y; Koji T; Aoyagi T; Maeda K; Eguchi K
CORPORATE SOURCE: First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan.
SOURCE: IMMUNOLOGY, **(1998 Sep)** 95 (1) 38-46.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128

AB **Apoptosis** of synovial cells in rheumatoid arthritis (RA) synovium determined in vivo is suggested to counteract the overgrowth of synovium. Immunohistological examination has revealed the infiltration of activated CD4+ T cells, which express Fas ligand (FasL), in RA synovium. The presence of a putative antigen (Ag) of autoimmune disorders in a target organ may induce the activation of specific T cells in the inflammatory region such as RA synovium. We examined the possible role of CD4+ T cells activated by synovial cells in a staphylococcal enterotoxin B (SEB)-dependent manner, inducing synovial cell **apoptosis**. Synovial cells were cultured with or without interferon-gamma (IFN-gamma) and further incubated with CD4+ T cells in the presence of SEB. After the cocultivation, both the cytotoxicity and FasL expression of CD4+ T cells were investigated. Constitutive Fas expression was detected on both unstimulated and IFN-gamma-stimulated synovial cells. CD4+ T cells did not kill SEB-pulsed unstimulated synovial cells efficiently. In contrast, when CD4+ T cells were incubated with IFN-gamma-stimulated synovial cells with SEB whose human leucocyte antigen (HLA)-DR and -DQ expression was markedly induced, significant cytotoxicity by these cells against synovial cells was detected. The addition of **anti-HLA-DR** and -DQ monoclonal antibodies (mAbs) or human Fas chimeric protein (hFas-Fc) reduced this cytotoxicity. FasL expression of CD4+ T cells cocultured with IFN-gamma-stimulated synovial cells with SEB was significantly induced. Furthermore, the addition of mAbs against CD54, CD58 and CD106 inhibited both the cytotoxicity and FasL expression of CD4+ T cells induced by IFN-gamma-stimulated synovial cells in the presence of SEB, indicating the importance of costimulatory molecules on synovial

cells in activating CD4+ T cells. Our results suggest that CD4+ T cells are activated by synovial cells by an SEB-dependent manner and express FasL, inducing Fas-mediated **apoptosis** of the latter cells. These phenomena may regulate the overgrowth of synovial cells in RA synovium.

L27 ANSWER 14 OF 18 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97461438 MEDLINE
DOCUMENT NUMBER: 97461438 PubMed ID: 9317119
TITLE: HLA-DR-triggered inhibition of hemopoiesis involves Fas/Fas ligand interactions and is prevented by c-kit ligand.
AUTHOR: Lee J W; Gersuk G M; Kiener P A; Beckham C; Ledbetter J A; Deeg H J
CORPORATE SOURCE: Transplantation Biology Program, Fred Hutchinson Cancer Research Center, Seattle, WA 98104, USA.
CONTRACT NUMBER: CA18029 (NCI)
CA18221 (NCI)
HL36444 (NHLBI)
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 Oct 1)** 159 (7) 3211-9.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 19971105
Entered Medline: 19971021

AB The function of MHC class II (HLA-DR) Ags in hemopoiesis is not well defined. Here we investigated the effect of **anti-HLA-DR** mAb H81.9 on human marrow cells. mAb H81.9 inhibited colony formation from purified CD34+ marrow cells in long term culture-initiating cell assays. Inhibition was prevented, however, if c-kit ligand (stem cell factor (SCF)) was added to cultures concurrently with H81.9. DNA histograms from cultured untreated marrow mononuclear cells showed 2+/-1.2% **apoptotic** nuclei, whereas 14.1+/-5.4% were **apoptotic** after 12-h exposure to mAb H81.9. The **apoptotic** peak was reduced to 1.2+/-0.8% when SCF was added to cultures concurrently with mAb H81.9. The addition of Fas-Ig, a fusion protein that neutralizes Fas ligand (Fas-L), also prevented mAb H81.9-induced **apoptosis**. As determined by terminal deoxynucleotidyl transferase assays, agonistic anti-Fas mAb also induced **apoptosis** (in 13+/-4% of cells), and combined treatment with anti-Fas mAb and H81.9 was additive (27% **apoptotic** nuclei). The extent of **apoptosis** induced by anti-Fas mAb was significantly reduced by SCF. After H81.9 exposure, Fas was up-regulated on CD34+ cells, and Fas-L expression was 2.5-fold higher than in controls or CD34- cells, particularly within a small cell window with low orthogonal scatter (lymphocyte gate). These findings show that HLA-DR-mediated signals inhibit hemopoiesis in human marrow by a mechanism involving Fas/Fas-L-dependent signals that are blocked by c-kit ligand. These data suggest a possible role for MHC class II molecules in the regulation of hemopoiesis.

L27 ANSWER 15 OF 18 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1998042470 MEDLINE
DOCUMENT NUMBER: 98042470 PubMed ID: 9367846
TITLE: Fas/Fas ligand interaction regulates cytotoxicity of CD4+ T cells against staphylococcal enterotoxin B-pulsed endothelial cells.
AUTHOR: Urayama S; Kawakami A; Matsuoka N; Tsuboi M; Nakashima T; Kawabe Y; Koji T; Eguchi K
CORPORATE SOURCE: First Department of Internal Medicine, Nagasaki University School of Medicine, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Oct 29)** 239 (3) 782-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971212

AB Infiltration of activated CD4+ T cells and **apoptosis** of endothelial cells are present in the synovium of rheumatoid arthritis (RA). Using staphylococcal enterotoxin B (SEB) as an antigen, we examined the possible role of antigen (Ag)-dependent activation of CD4+ T cells by endothelial cells, in inducing endothelial cell **apoptosis**. The human endothelial cell line, EA.hy926 cells, was cultured with or without interferon-gamma (IFN-gamma) and further incubated with CD4+ T cells in the presence or absence of SEB. After this cocultivation, the cytotoxicity and Fas ligand (FasL) expression of CD4+ T cells were examined. A small percentage of EA.hy926 cells expressed HLA-DR and -DQ, and this expression was significantly augmented after IFN-gamma stimulation. Anti-Fas IgM-induced **apoptosis** was exhibited by both unstimulated and IFN-gamma-stimulated EA.hy926 cells. Cytotoxicity of CD4+ T cells toward SEB-pulsed unstimulated EA.hy926 cells was detected. Furthermore, when CD4+ T cells were incubated with IFN-gamma-stimulated, SEB-pulsed EA.hy926 cells with augmented HLA-DR and -DQ expression, this cytotoxicity was more significant. The addition of **anti-HLA-DR** and -DQ monoclonal antibodies (mAbs) or human Fas chimeric protein (hFas-Fc) reduced the cytotoxicity. FasL expression was induced in CD4+ T cells cocultured with SEB-pulsed EA.hy926 cells, especially when the EA.hy926 cells were IFN-gamma-stimulated. Furthermore, the addition of mAbs against CD54 and CD58 inhibited both the cytotoxicity and FasL expression of CD4+ T cells induced by SEB-pulsed EA.hy926 cells, indicating the importance of costimulatory molecules on EA.hy926 cells in activating CD4+ T cells. Our results suggest that CD4+ T cells are activated by endothelial cells in an Ag-dependent manner and subsequently express FasL, which induces Fas-mediated **apoptosis** of endothelial cells. This phenomenon may counteract the growth of RA synovium by inhibiting the proliferation of endothelial cells.

L27 ANSWER 16 OF 18 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998029877 MEDLINE
DOCUMENT NUMBER: 98029877 PubMed ID: 9363450
TITLE: Down-regulation of CD95 (Fas/Apo-1) in the epithelia of adenovirus-infected appendices.
AUTHOR: Larousserie F; Berrebi D; Florentin A; De Lagausie P; Aigrain Y; Peuchmaur M
CORPORATE SOURCE: Service d'Anatomie et de Cytologie Pathologiques, Hopital Robert Debre, Paris, France.
SOURCE: HISTOPATHOLOGY, **(1997 Oct)** 31 (4) 342-6.
Journal code: 7704136. ISSN: 0309-0167.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971222

AB AIMS: Adenoviral inclusions are commonly seen in appendices from infants with intussusception. They are associated with focal epithelial budding and less frequently with epithelial shedding. These morphological changes could depend on the opposing effects of adenoviral gene products on CD95-mediated **apoptosis**. METHODS AND RESULTS: Appendices from intussusceptions with viral inclusions (n = 4) and normal appendices (n = 10) were studied by immunochemistry with anti-adenovirus, anti-CD95 and **anti-HLA-DR** antibodies. **Apoptosis** was studied by the TUNEL method. The mucosa of normal appendices contained no adenoviral protein. CD95 was present in all epithelial cells except Paneth cells. HLA-DR was absent in epithelial cells and **apoptosis** was seen only in germinal centres and in a few surface epithelial cells. The epithelium of appendices from intussusceptions contained nuclear inclusions labelled with anti-adenovirus antibody, always found in the epithelial buds. The epithelial CD95 pattern was drastically altered in adenovirus-infected appendices. CD95 was absent from the budding foci. In these foci, HLA-DR was overexpressed. There was also increased epithelial **apoptosis** in areas remote from those lacking CD95 antigen. CONCLUSIONS: The appearance of epithelial budding or shedding in appendices from intussusception could be due to focal in situ differences in the expression of adenoviral genes.

L27 ANSWER 17 OF 18 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 97351080 MEDLINE
DOCUMENT NUMBER: 97351080 PubMed ID: 9207456
TITLE: HLA-DR-mediated signals for hematopoiesis and induction of **apoptosis** involve but are not limited to a nitric oxide pathway.
AUTHOR: Lee J W; Beckham C; Michel B R; Rosen H; Deeg H J
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, and the Department of Medicine, University of Washington, Seattle 98104, USA.
CONTRACT NUMBER: CA18029 (NCI)
CA18221 (NCI)
HL36444 (NHLBI)
+
SOURCE: BLOOD, **(1997 Jul 1)** 90 (1) 217-25.

Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19970805
Entered Medline: 19970722

AB Cross-linking of major histocompatibility complex (MHC) class II antigens by **anti-HLA-DR** monoclonal antibody (MoAb; H81.9; IgG2a) results in inhibition of hematopoiesis in canine and human models. Inhibition of hematopoiesis is associated with **apoptosis** in a proportion of marrow cells. Since in murine macrophages class II cross-linking triggers nitric oxide (NO) production, and NO is thought to affect regulation of hematopoiesis, we investigated whether NO was involved in our models. In murine J774 monocytes/macrophages, MoAb H81.9 did induce NO. NO production was blocked by N(G)-monomethyl-L-arginine (NMMA), an inhibitor of NO synthase (NOS), and by the antioxidant N-acetylcysteine (NAC). In human and canine long-term marrow cultures (LTMCs) and in enriched marrow monocytes, however, no measurable increase in NO production was noted after H81.9 exposure. Nevertheless, NAC protected LTMCs against H81.9 induced inhibition of hematopoiesis. Therefore, we determined the effect of an exogenous NO donator, sin-1 (3-morpholinosydnonimine), on canine and human LTMCs and on **apoptosis**. Sin-1 at concentrations > or =100 microg/mL inhibited LTMCs and induced **apoptosis**; at low concentrations (1 microg/mL), however, sin-1 stimulated the generation of colony-forming unit granulocyte-macrophage. Combined treatment with sin-1 at 100 microg/mL and MoAb H81.9 resulted in profound inhibition of hematopoiesis in both canine and human LTMCs, and had an additive effect on **apoptosis**. At 1 microg/mL sin-1 counteracted the effect of H81.9 on hematopoiesis. The effect of sin-1 on **apoptosis** and hematopoiesis in LTMC was largely prevented by NAC. These results are consistent with the hypothesis that HLA-DR mediated **apoptosis** and inhibition of hematopoiesis involve oxidative stress. However, the biphasic response of hematopoiesis to sin-1 suggests a complex regulatory network possibly related to differences in NO sensitivity of distinct subpopulations of cells. Signals in addition to NO appear to be involved in the effect of **anti-HLA-DR** MoAb on hematopoiesis.

L27 ANSWER 18 OF 18 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 96232975 MEDLINE
DOCUMENT NUMBER: 96232975 PubMed ID: 8655363
TITLE: Cytolytic effector mechanisms of human CD4+ cytotoxic T lymphocytes.
AUTHOR: Susskind B; Shornick M D; Iannotti M R; Duffy B; Mehrotra P
T; Siegel J P; Mohanakumar T
CORPORATE SOURCE: Department of Surgery, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: AI26934 (NIAID)
SOURCE: HUMAN IMMUNOLOGY, **(1996 Jan)** 45 (1) 64-75.
Journal code: 8010936. ISSN: 0198-8859.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960808
Last Updated on STN: 19960808
Entered Medline: 19960730

AB To elucidate mechanisms by which human CD4+ cells mediated cytolytic activity, we studied the expression of cytolytic proteins and the effects of inhibitors and mAbs on T-cell clones. Of seven cytolytic CD4+ clones, three were specific for the HLA-DR17, while four recognized DR18. **Anti-HLA-DR** mAb and anti-CD4 mAb blocked lysis. In addition, N alpha-p-tosyl-L-lysine chloromethylketone (TLCK), a serine esterase inhibitor, as well as cytochalasin B and monensin, antagonists of secretory pathways, inhibited CD4+ CTLs, whereas the absence of extracellular Ca+2 or the presence of Ca+2 channel blockers partially inhibited cytotoxicity. CD4+ CTLs induced **apoptosis** of target cell nuclei and membrane damage simultaneously. The CD4+ clones synthesized perforin and granzyme B and expressed the granule-associated protein TIA-1. Our studies indicate that two distinct mechanisms may contribute to cytolysis by CD4+ clones: (1) a Ca+2-dependent mechanism associated with the cytotoxic granules and (2) a Ca+2-insensitive mechanism.